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OSMOLAR CONTROL OF THE CIRCULATION IN HEMORRHAGIC HYPOTENSION

An experimental study in the cat

By
Johannes Järhult

Lund 1975

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From the Department of Physiology and Biophysics,

University of Lund,

Sweden.

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This thesis is based mainly on the following publications:

I. JÄRHULT, J., J. LUNDVALL, S. MELLANDER and S. TIBBLIN, Osmolar control of plasma volume during hemorrhagic hypotension. Acta physiol. scand. 1972. 85. 142-144.

II. JÄRHULT, J., Osmotic fluid transfer from tissue to blood during hemorrhagic hypotension. Acta physiol. scand. 1973. 89. 213-226.

III. JÄRHULT, J. and P.-O. GRÄNDE, Transcapillary fluid movements in sympathectomized intestine and skin during hemorrhagic hypotension. Acta physiol. scand. 1975. In press.

IV. JÄRHULT, J., Role of the sympatho-adrenal system in hemorrhagic hyperglycemia. Acta physiol. scand. 1975. 93. 25-33.

V. JÄRHULT, J. and S. MELLANDER, Autoregulation of capillary hydrostatic pressure in skeletal muscle during regional arterial hypo- and hypertension. Acta physiol. scand. 1974. 91. 32-41.

VI. JÄRHULT, J., J. HILLMAN and S. MELLANDER, Circulatory effects evoked by 'physiological' increases of arterial osmolality. Acta physiol. scand. 1975. 93. 129-134.

In the text, these papers are referred to by their Roman numerals.

Chapter 1

INTRODUCTION

Hemorrhage implies a stress situation for the organism which is met by compensatory mechanisms that often are capable of restoring cardiovascular homeostasis. If the compensation is insufficient and, in particular, if secondary circulatory derangements or other complications occur, hemorrhagic shock may finally ensue. Various aspects of the latter topic have been reviewed previously, for instance by Wiggers (1950), Seeley and Weisiger (1961), Bock (1962), Hershey (1964), Fine (1965), Mills and Moyer (1965) and Weil and Shubin (1967).

The present study deals with compensatory adjustments occurring in early stages of hemorrhage, with particular reference to the development of plasma hyperosmolality and its role in cardiovascular control.

The defence mechanisms in bleeding are primarily aimed at limiting the deleterious effects of hypovolemia on tissue perfusion and nutrition. The rapid augmentation of sympathetic discharge leading to improved cardiac performance, increased peripheral resistance, and constriction of the capacitance vessels constitutes an important first line of defence, but can cause no definite restoration. The adequate compensation of course implies a replacement of the shed blood volume. The restitution of the red cell volume is, however, a slow physiological process and, therefore, the refill of the circulatory system in the early stages of hemorrhage must be accomplished by an increased plasma volume.

Previous studies have revealed different mechanisms for such restoration of plasma volume in hypovolemia. Most important, perhaps, is a transcapillary absorption of interstitial fluid mediated by an adrenergic reflex resetting of the pre-/postcapillary resistance ratio which lowers hydrostatic capillary pressure in muscle and skin tissues (Öberg 1964). More gradual

adjustments are accomplished by the endocrine and reflex regulation of renal water and salt excretion (cf. Wiggers 1950, Laragh and Sealey 1973) and by control of the fluid intake via the thirst mechanism (cf. Fitzsimons 1972).

The present investigation in cats indicated that in hemorrhage there is also an important osmolar control of plasma volume related to substances other than the plasma proteins. In fact, this regulatory mechanism seems primarily aimed at an overall restoration of extracellular fluid volume effected by osmotic fluid withdrawal from the intracellular space. A similar control principle was recently shown to be operating in heavy exercise (Lundvall, Mellander, Westling and White 1972).

It will be demonstrated that hemorrhagic hypotension is associated with a pronounced increase of blood osmolality (Chapter 3), in turn mainly caused by glucose release from the liver (Chapter 4). The reflex control mechanisms for this glucose liberation are described in Chapter 5. That the blood-borne hyperosmolality leads to a transcapillary osmotic absorption of extravascular fluid into the blood stream is shown in Chapter 6 and this process occurs mainly in skeletal muscle and skin tissues. From a quantitative point of view, the osmolar plasma volume control seems to be as important as the previously known adrenergic reflex mechanism, at least in severe hemorrhage. Plasma volume expansion by fluid absorption does not result from the arterial hypotension per se, since, as described in Chapter 7, the expected passive fall of capillary hydrostatic pressure is effectively prevented by local vascular autoregulatory mechanisms. Finally, it is shown that the hemorrhagic hyperosmolality exerts some inhibitory action on the tone of the resistance vessels in several tissues and concomitantly a moderate positive inotropic action on the heart (Chapter 8).

Chapter 2

METHODOLOGY

Material and anesthesia

Experiments were performed on a total of 143 cats of both sexes (mean weight 3.2 kg) anesthetized intravenously with α-chloralose (50 mg/kg b.wt.) after induction with ether. The majority of the cats also received an initial small dose of pentobarbital sodium (5-20 mg). In some pilot experiments, the anesthesia was supplemented with urethane (100 mg/kg b.wt). The animals were kept on a normal mixed diet and fasted for about 16 hr before the experiments, but received water ad libitum.

Surgical procedures

Vascular reactions were studied in four different tissues, viz. skeletal muscle, skin, intestine, and kidney.

Skeletal muscle preparation. Studies were performed on the lower leg muscles (below called calf muscles) in 81 cats and the region was prepared according to the technique described by Kjellmer (1964). In brief, the skin of the right hind leg was dissected free from the underlying muscle tissues down to the ankle and the paw removed at the ankle joint. The thigh muscles were separated from the lower leg. The bone marrow cavity of the distal femur was drilled open and plugged with cotton soaked in silicone grease to occlude intra-osseous vascular connections. Small vessels between the thigh and lower leg were ligated so that the popliteal artery and vein formed the sole vascular connections with the main part of the body. With a few exceptions (II,VI), the muscle region was acutely sympathectomized by cutting the sciatic nerve. The popliteal vein was cannulated and the outflow diverted to the external jugular vein via an optical drop recorder unit. When changes of tissue volume were to be recorded, the muscle preparation was enclosed in a waterfilled, temperature-controlled (38°C) plethysmograph, using the skin flap for proximal closure.

In some experiments (I,II,V), the arterial inflow to the calf muscles was diverted from the proximal femoral artery via a T-tube shunt to the popliteal artery to permit local injections of drugs and precise measurements of arterial inflow pressure. In 9 of these experiments (II), a perfusion pump (Harvard, model 1210) was inserted in the shunt to allow ad-

justments of the regional blood flow to desired levels. In the hypotension experiments described in paper V, the regional arterial inflow pressure was manually adjusted by a screw clamp proximal to the T-tube.

Skin preparation. The hind paw was chosen for studies of the circulatory events in a 'cutaneous' vascular bed (20 cats). To observe reactions mainly in 'nutritive' skin vessels, the pads (with their abundant arterio-venous anastomoses) were excluded from the circulation by tight ligatures. The skin of the calf was dissected free from the knee down to the ankle joint. All superficial and deep veins were ligated 1-2 cm above the joint, except for the great saphenous vein. This vessel was cannulated and its outflow diverted to the jugular vein via an optical drop recorder. In some experiments (VI), drainage through deep veins was prevented by an ankle cuff, the pressure in which was raised slightly above venous outflow pressure. When desired, the paw was sympathectomized by severing the sciatic and the femoral nerves. To record changes in tissue volume (III), the paw was placed in a perspex plethysmograph filled with water, using the calf skin flap for proximal closure. The water temperature was kept at 34°C (≈neutral temperature). - In two experiments (III), the circulatory events in the paw were studied during regional hypotension. For this purpose, a short shunt circuit was inserted between the femoral and popliteal artery, all other arterial vessels between the thigh and the calf being ligated. Regional arterial pressure was then monitored from a T-tube in the shunt and could be adjusted to desired levels by a screw clamp.

Intestinal preparation. In 16 cats without signs of intestinal infection, a preparation of the small intestine was made, the principle of which has been described by Folkow et al. (1963). In brief, a segment of the jejunum (weighing 15-30 g) was isolated and the remainder of the intestines removed. With some exceptions (VI), the regional autonomic nerves were ligated and cut. The venous outflow from the segment and its lymph node was measured with an optical drop recorder and returned to the animal via the external jugular vein. To record changes in tissue volume (III), the intestinal preparation was enclosed in a perspex, temperature-controlled (38°C) plethysmograph filled with Tyrode's solution. A short arterial shunt circuit was inserted in the superior mesenteric artery in these plethysmographic experiments. Closure of the plethysmograph at the site of the entrance of the two cognate vessels was accomplished with silicone grease.

Kidney. Blood flow from the left kidney was recorded in 8 experiments (VI). After ligation of the left spermatic or ovarian vein, the main renal vein was cannulated and the venous outflow diverted via an optical drop re-

corder to the external jugular vein. The regional sympathetic nerves were ligated and cut in 3 of these experiments.

Interference with the sympatho-adrenal system. Observations of vascular reactions were made in the different regions both with intact sympathetic innervation and after regional sympathectomy. In the latter experiments, phenoxybenzamine (1-4 mg) was given close arterially to prevent an influence from circulating catecholamines. Significant systemic effects of the blocking drug was avoided by collecting and discarding the venous outflow for about 3 min after the injection. This volume of blood was substituted by the same amount of isotonic dextran-Tyrode solution. The effectiveness of the α-blockade was checked by a close arterial injection of noradrenaline (5-10 µg/kg b.wt.).

In paper IV, special attention was paid to the influence of different links in the sympatho-adrenal system on the glucose release from the liver during hemorrhage. This analysis was performed on 33 cats divided into 4 different groups. In 14 cats the sympatho-adrenal system was left intact; in 7 cats the adrenal glands were carefully removed; in 6 cats the hepatic nerve plexus was dissected free around the hepatic artery and portal vein, ligated and cut; in 6 cats the major and minor splanchnic nerves were severed bilaterally and, in addition, both adrenals removed.

Catheterization techniques for blood sampling. Before catheterization, the animals were heparinized (750 - 1000 IU/kg b.wt.). In most of the present experiments, blood samples were taken for determinations of plasma osmolality and plasma glucose concentration. Arterial samples were withdrawn from a catheter in the right carotid artery and venous samples from the outflow catheters in the four different regions (see above). In paper IV, an analysis was made of the role of the liver in the hemorrhagic hyperglycemia response by determining glucose, osmolality, and glucagon levels in plasma from various sites in the venous system. For this purpose, two fine siliconized polyethylene catheters were inserted into the inferior caval vein via the two major saphenous veins. One of these was advanced until its tip was positioned just above the iliac bifurcation (below called 'iliac' vein) and the other one to a site just above the entrance of the hepatic vein (below called 'hepatic' vein). In some of the experiments (n=7), a fine catheter was also inserted into the portal vein via cannulation of a distal branch of the superior mesenteric vein.

Cardiovascular recordings

Mean (and sometimes pulsatile) arterial blood pressure was measured with

Statham P23 AC transducers placed at heart level. The pressure was monitored from the right carotid artery or (in paper III) from the left femoral artery. Regional venous outflow pressures were determined from the height of the outflow tubing above heart level or, sometimes (V), measured directly with a Statham P23 DC transducer from a T-tube placed close to the cannula in the popliteal vein. The transducer was then positioned at the water level in the plethysmograph to compensate for the induced external water pressure. In some of the hypotension experiments (V), the pressures in a small muscle artery (SAP) and a small muscle vein (SVP) were monitored from drawn-out flexible nylon tubings inserted in the sural artery and vein and recorded with Statham transducers (for details see Haddy et al. 1954, Lundvall 1972).

Heart rate was recorded with a Grass tachograph triggered by the systolic pressure wave (VI).

The regional blood flows were continuously registered with silicone-filled optical drop recorder units inserted on the venous side (Lindgren 1958).

Changes of the tissue volume were recorded with the plethysmographic technique originally described by Mellander (1960). The plethysmograph design was modified to fit the various tissues. In some early experiments (I,II), changes of tissue volume were registered with a piston-recorder and later (III,V) with an electronic gravimetric transducer (Grass FT 10; for details see Grände et al. 1974).

The cardiovascular parameters were usually recorded on a Grass polygraph or, occasionally, on a kymograph.

Analysis of peripheral vascular functions

Regional vascular resistance was derived from the arterio-venous pressure gradient and regional blood flow and expressed as mm Hg/(ml/min x 100 g tissue).

Data on capacitance responses and net transcapillary fluid movements were derived from the observed changes of tissue volume according to the principle described by Mellander (1960). This implies that abrupt changes of tissue volume, coordinated in time with changes of vascular resistance, are considered to reflect the responses of the capacitance vessels, whereas gradual changes of tissue volume, occurring in face of a maintained steady state resistance response, are considered to represent net transcapillary fluid movements. This interpretation of the volume curve has been validated

in several studies by the simultaneous use of radioactive tracer techniques (e.g. Åblad and Mellander 1963, Kjellmer 1965).

Reactions of the precapillary sphincters were estimated with the capillary filtration coefficient (CFC) method (Cobbold et al. 1963, Folkow and Mellander 1970). The venous pressure increase applied during determinations of the CFC was less than 5 mm Hg in these experiments to minimize myogenic reactions (cf. Mellander et al. 1964). Unless otherwise stated, a ratio of pre-/postcapillary resistance of 4/1 was used for the CFC calculations (Pappenheimer and Soto-Rivera 1948).

Soft tissue weight of the studied regions was determined at the end of the experiment.

Spread of data is given as the standard error of the mean. Significance tests were performed according to Student's t-test.

Biochemical analyses

Plasma osmolality was determined with thermistor cryoscopy (Osmometer 31 LAS, Advanced Instruments, Inc.). Each sample was measured twice and the mean value used. Repetitive readings on osmolar standards deviated at most by 1.5 mOsm/kg H_2O from the true value.

Plasma glucose concentration was determined by the glucose-oxidase technique.

Plasma glucagon concentration (immuno-reactive glucagon) was estimated with a radio-immuno-assay technique developed by Nilsson and Wallensten (1975).

Plasma sodium and potassium concentrations were determined with flame photometry.

Plasma urea concentration was determined with the Technicon Autoanalyzer System.

Experimental procedures

Hemorrhagic hypotension experiments. The animals rested for about 30 min after the completion of the surgical preparations. At the end of this control period, arterial and venous blood samples were withdrawn for biochemical determinations. In the plethysmographic studies (I-III,V) venous outflow pressure in the different regions was set so as to establish, approximately, an isovolumetric state in the control situation (Starling equilibrium).

Hemorrhagic hypotension was achieved by bleeding the animal into a sili-

conized pressure bottle connected via a T-tube to the right carotid artery. The exsanguination was rapid so that arterial blood pressure reached a level of 50 mm Hg within 3 min. This pressure level was then maintained throughout the experiment with the aid of the pressure bottle. Changes of the peripheral vascular functions in the different regions were followed during the hypotensive period which in most cases lasted for 90 min. Repetitive arterial and venous blood samples were taken for biochemical analyses during the period of hypotension. The animals breathed spontaneously throughout the experiments.

Some comments will be given here concerning the abovementioned experimental hemorrhage model. This model was originally developed in Wiggers laboratory (Werle et al. 1942) and has later been extensively used. It implies that the animal is kept at a constant hypotensive level irrespective of compensatory adjustments. The model has several advantages. For instance, it permits detailed studies of net transcapillary fluid movements without interference from a fluctuating arterial inflow pressure and venous outflow pressure, which aided in the interpretation of the present results. The analysis of capillary fluid transfer during bleeding was furthermore facilitated in the present experiments by blockade of the lymph drainage from the studied regions. It should be made clear, however, that this bleeding model creates an "artificial" hemorrhagic situation insofar that the animal cannot benefit from the effects of the compensatory mechanisms that normally tend to restore blood pressure and volume. Animals with vivid sympatho-adrenal reflexes will therefore be exposed to a more intense vasoconstriction and, hence, to a greater blood loss than those with less effective reflex mechanisms (cf. Chien 1967). This was noticed in the present experiments in terms of a relatively wide range of the volume of shed blood. Thus, the fraction of total blood volume (assumed to be 7 per cent of the body weight in the control situation, see Altman and Dittmar 1971) which had to be withdrawn initially to lower blood pressure to 50 mm Hg varied in the different animals from 11-35 per cent (mean value 26 ± 2 %).

Cardiovascular and biochemical analyses were also performed in a few sham operated animals prepared as described above for the skeletal muscle region. These animals were not bled after the initial control period, but left undisturbed for 90 min.

Regional hypotension experiments. The transition from normo- to hypotension in the hemorrhage experiments causes a marked change of the perfusion gradient and the transmural pressure in the peripheral vascular beds. To analyse possible local effects of such pressure alterations per se, re-

gional hypotension experiments were performed (III,V) in the following way: The abovementioned vascular functions were observed in response to regional arterial hypotension of varying duration, accomplished by adjustments of a screw clamp placed on the cognate artery to the region (skeletal muscle and paw). Vascular resistance and CFC were determined in the isovolumetric control period of normotension, and the effects on vascular resistance, capacitance, CFC, and net transcapillary fluid transfer were followed during periods of graded regional arterial hypotension (range down to 30 mm Hg). In one series of these experiments, arterial pressure in the muscle region was kept at 50 mm Hg for a period of 90 min and arterial and regional venous plasma osmolality was determined at intervals. In some other experiments, papaverine (0.6-1.6 mg/min) was infused close arterially to abolish vascular tone and, hence, active local responses to the regional hypotension.

An analysis of local vascular effects in skeletal muscle was also performed during short-term periods of arterial hypertension up to 170 mm Hg. The hypertension was evoked by bilateral carotid occlusion after cervical vagotomy. Alpha-adrenergic effects in the studied muscle region were then prevented by regional sympathectomy and by close arterial administration of phenoxybenzamine (10 mg/kg muscle tissue).

Hypertonic infusion experiments. As will be shown, hemorrhage leads to an increase of the plasma osmolality. In an attempt to study selectively the effects of plasma hyperosmolality per se on cardiovascular functions, hypertonic solutions were infused intravenously to resting non-bled animals at a rate which increased the arterial osmolality to about the same levels as in the present hemorrhage experiments. Hypertonic (30-50 %) solutions of glucose, sucrose, or xylose were then slowly infused via the right axillary vein at a rate of 0.3-1.0 ml/min. In one series of these experiments (VI), the effects on vascular resistance in muscle, skin, intestine, and kidney and on mean and pulsatile arterial pressure and heart rate were observed. The hypertonic infusions lasted for 5 min and were repeated at intervals 2-3 times in each animal. The cardiovascular parameters and arterial plasma osmolality were analysed before, during, and for 15 min after the hypertonic infusions. In another series of hypertonic infusion experiments (Chapter 6 and paper III), the effects on net transcapillary fluid movement in the sympathectomized skeletal muscle, paw, and intestine were observed. Hypertonic glucose (30 %) was slowly infused for 10-30 min in these experiments and arterial and regional venous osmolality determined at intervals. The adrenals were removed in these experiments to exclude effects of possible release of cathecolamines.

Chapter 3

CHANGE OF PLASMA OSMOLALITY DURING HEMORRHAGIC HYPOTENSION

(Paper I-IV)

General considerations

Little attention has been paid to the problem of osmolar changes in hemorrhage. In 1963 Brooks et al. reported that the arterial plasma osmolality in dogs was virtually unchanged after 90 min of hemorrhagic hypotension at a level of 40 mm Hg. They found, however, an increase of the plasma glucose concentration, and explained the plasma isotonicity by an 'equi-osmolar' drop of the plasma sodium concentration. Bergentz and Brief (1965), on the other hand, demonstrated that severe hemorrhage in dogs in fact could be associated with a considerable increase of the arterial plasma osmolality, in their experiments amounting to about 25 mOsm/kg H_2O after 20 min of arterial hypotension at 20 mm Hg. This finding in dogs was confirmed some years later by Baue et al. (1967), Boyd and Mansberger (1968), and Grega et al. (1971), although in the latter study the hyperosmolality was more moderate. Boyd and Mansberger revealed a hyperosmolar state also in humans in hemorrhagic shock.

The patho-physiological significance of the hemorrhagic hyperosmolality is poorly understood. Boyd and Mansberger (1968) considered the hyperosmolality in dogs and patients to be a bad prognostic sign insofar that they found an impaired survival in individuals with marked plasma hypertonicity in hemorrhagic shock. On the other hand, Brooks et al. (1963), Bergentz and Brief (1965), and Baue et al. (1967) found that the survival rate in dogs was improved if the animals received a hypertonic instead of an isotonic infusion in the oligemic phase of hemorrhagic hypotension. The mechanism for such a beneficial effect, however, could not be revealed in these studies.

The hypothesis is advanced that the organism might benefit from the plasma hyperosmolality during hemorrhage insofar that it might cause an osmotic fluid absorption from the extravascular to the intravascular space with a consequent increase of plasma volume. Such a mechanism has recently been shown to be operating in heavy exercise (Lundvall et al. 1972). An osmotic withdrawal of tissue fluid in bleeding would be possible, however, only if the plasma osmolality exceeds the tissue osmolality, i.e. if the hyperosmolality is primarily blood-borne. As a first approach to this problem, detailed studies of arterial and venous plasma osmolality were performed during hemorrhagic hypotension.

Present results

Concomitant determinations of arterial and venous plasma osmolality during hemorrhagic hypotension at 50 mm Hg were made in 73 cats with intact sympatho-adrenal system (I-IV and unpublished experiments). Arterial samples were always taken from the carotid artery, whereas the venous samples represented different tissues, viz. skeletal muscle and skin, intestine, kidney, and liver.

Fig. 1 shows collected data from 63 cats on the osmolar changes in a skeletal muscle-skin region. The venous samples in this series were taken from different sites: popliteal vein (n=36), femoral vein (n=9), great saphenous vein (n=8), and iliac vein (n=10). The osmolality changes at these various sites in the venous system were not significantly different from each other and the data have therefore been pooled (Fig. 1). In the control period, arterial plasma osmolality averaged 319 ± 0.7 and venous plasma osmolality 321 ± 0.7 mOsm/kg H_2O (in agreement with Lundvall 1972). It can be seen from Fig. 1 that hemorrhage caused a marked increase of the arterial plasma osmolality with the most rapid change in the initial 10 min of hypotension. A clearcut increase could be detected as early as 45 sec after the start of

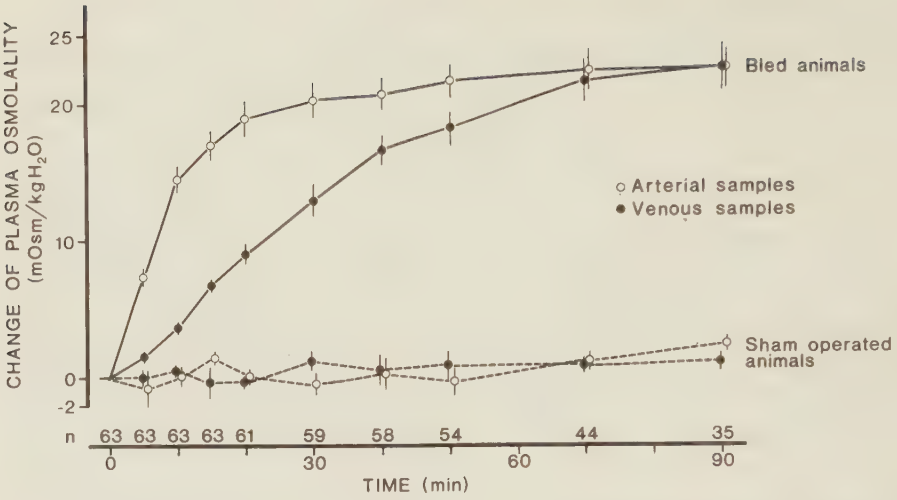

FIG. 1: Changes from control value of arterial and popliteal venous plasma osmolality (mean values ±S.E.) in cats bled to 50 mm Hg (n=63) and in sham operated cats (n=4).

the bleeding. The arterial hyperosmolality reached a value of about 20 mOsm/kg H_2O above control after 20 min, a level then maintained throughout the 90 min period of observation. Venous plasma osmolality, on the other hand, rose more gradually and did not reach the arterial level until some 60 min after the start of the hemorrhagic hypotension. A positive arterio-venous osmolar difference (implying a transcapillary osmolar gradient, see below) was thus present during the first hour, though most pronounced during the initial 30 min of hypotension. The sham operated animals did not show any significant alteration of arterial or venous osmolality. - In some experiments (I), the changes of arterial and venous plasma osmolality were observed during a more prolonged (3 hr) period of hemorrhagic hypotension at 50 mm Hg. These experiments showed that the hyperosmolality remained approximately constant at the high level throughout this period. During the last hour, venous osmolality tended to slightly exceed arterial osmolality.

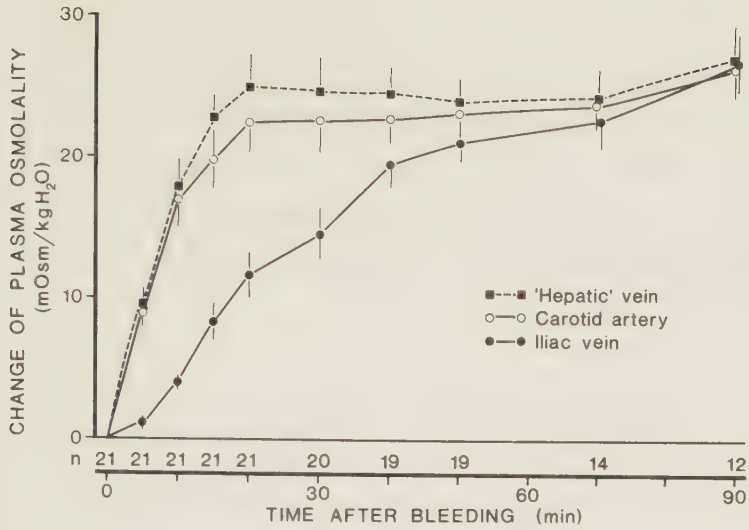

Fig. 2: Simultaneously determined plasma osmolality in the 'hepatic' venous, arterial, and iliac venous blood during hemorrhagic hypotension at 50 mm Hg for 90 min. Mean values ±S.E. given.

Data for the intestinal (n=8) and renal (n=2) circulations showed that the osmolality pattern was basically similar to that described in Fig. 1, insofar that the arterial osmolality was higher than the regional venous osmolality in the initial period of hypotension. In these tissues, however, venous osmolality approached arterial osmolality much earlier than in skeletal muscle and skin, viz. after 30 min in the intestine and within less than 10 min in the kidney. The difference can be ascribed to the much higher blood flow in intestine and kidney than in muscle.

The osmolar changes in venous samples from the 'hepatic' vein (see Methodology) were distinctly different from those taken from the tissues mentioned. From the very beginning of the bleeding, the 'hepatic' venous osmolality thus exceeded the concomitantly determined arterial osmolality and was much higher than that in the venous blood from the hindquarters (Fig. 2). On the other hand, the degree of hyperosmolality in the portal vein (n=7)

was much smaller than in the 'hepatic' vein.

It was concluded that the hemorrhagic hyperosmolality to a significant extent was caused by release of some substance(s) from the liver. It should be stressed, however, that the 'hepatic' venous blood was sampled in the inferior caval vein at the entrance of the hepatic vein, thus implying considerable admixture of blood from regions other than the liver. The magnitude of the true hepatic venous hyperosmolality therefore must have been underestimated in Fig. 2.

The data presented above refer to averages. Mention should be made that 6 animals out of the 73 did not respond with significant blood hyperosmolality during the hemorrhagic hypotension.

Comments

The present study has defined in detail the magnitude and the time course of the osmolar changes occurring in the arterial blood and in the venous effluent from several different tissues during hemorrhagic hypotension at 50 mm Hg. In the majority of the cats (92 %), hemorrhage evoked a rapid, pronounced (+20 mOsm/kg H_2O) and maintained increase of arterial osmolality, a finding in accordance with some previous observations in other species, including man (Bergentz and Brief 1965, Baue et al. 1967, Boyd and Mansberger 1968, Almli 1970, Boyd et al. 1970). Our analysis indicated, in addition, that the hemorrhagic hyperosmolality to a major extent was caused by release of some osmotically active product(s) from the liver. The nature of this substance will be described in Chapter 4.

This investigation was made under a standardized type of hemorrhage. Preliminary experiments indicated that the magnitude of the hyperosmolar response is related to the severity of the bleeding, which seems to explain some discrepancies reported in the previous literature (see above).

The patho-physiological significance of the hemorrhagic blood hyperosmo-

lality may be severalfold. As previously reported (Almli 1970), it might affect the fluid balance in the body via an influence on the thirst mechanism. It also seems to affect the 'internal' fluid balance by causing a redistribution of fluid from the intracellular to the interstitial and intravascular compartments (Chapter 6). Hemorrhagic hyperosmolality might also influence cardiac function and peripheral vascular resistance (Chapter 8).

Chapter 4

RELATION BETWEEN HYPEROSMOLALITY AND HYPERGLYCEMIA IN HEMORRHAGIC HYPOTENSION

(Paper II,IV)

General considerations

In 1877 Claude Bernard discovered that the glucose concentration in the blood rose in dogs subjected to hemorrhage, a finding later repeatedly confirmed in several species (see below). This suggested to us that glucose might be responsible to a significant extent for the hemorrhagic hyperosmolality described in the previous chapter and this hypothesis was tested in the present series of experiments.

Present results

From a few pilot experiments presented in Table I, it became evident that the hemorrhagic plasma hyperosmolality indeed was mainly caused by an increased glucose concentration. Thus it can be seen that the gradual rise of plasma osmolality, which after 70 min of hypotension exceeded the control value by 31 mOsm/kg H_2O, almost entirely could be attributed to the concomitant hyperglycemia. The potassium and urea concentrations also rose, but the osmolar effect of these changes was more than counterbalanced by the decrease in sodium concentration. Calculated values for the total osmolar change induced by these agents (neglecting the osmotic activity coefficients) are given at bottom of the table. These values agreed relatively well with the observed osmolar increase except at 70 min when the observed osmolar change somewhat exceeded the calculated value.

A more thorough investigation of the relation between the hyperosmolality and the hyperglycemia responses was made in 21 cats during hemorrhagic

TABLE I. Changes of osmolality, glucose, sodium, potassium, and urea-N in arterial plasma during hemorrhagic hypotension at 50 mm Hg (mean values from 2 cats). The approximate total change of osmolality due to glucose, sodium, potassium, and urea-N is depicted at bottom.

		Time of hypotension at 50 mm Hg		
	Control	10 min	30 min	70 min
Osmolality ($mOsm/kg\ H_2O$)	325.0	337.0 +12.0	344.5 +19.5	356.0 +31.0
Glucose (mM/L)	15.0	26.6 +11.6	38.9 +23.9	41.1 +26.1
Sodium (mEq/L)	152.0	147.0 -5.0	145.5 -6.5	144.5 -7.5
Potassium (mEq/L)	3.5	6.7 +3.2	6.0 +2.5	8.5 +5.0
Urea-N (mM/L)	3.3	3.6 +0.3	3.9 +0.6	4.1 +0.8
Calculated osmolality change ($mOsm/kg\ H_2O$)		+10.1	+20.5	+24.4

hypotension at 50 mm Hg of 90 min duration (Fig. 3). In the control period before bleeding, arterial plasma glucose concentration averaged 220 ± 15 mg% and venous plasma glucose concentration 210 ± 14 mg% in blood drained from the hindquarters, i.e. mainly representing skeletal muscle and skin tissues. It can be seen from Fig. 3 A that the arterial glucose concentration rose quickly and reached a level of 400 mg% above control after 30 min of hypotension. After this, there was a slight gradual decline to about 350 mg% above control 90 min after the start of the bleeding. The venous plasma glucose concentration increased more slowly and did not reach the arterial level until about 1 hour after the commencement of the hypotension. The clearcut difference between the arterial and venous plasma glucose con-

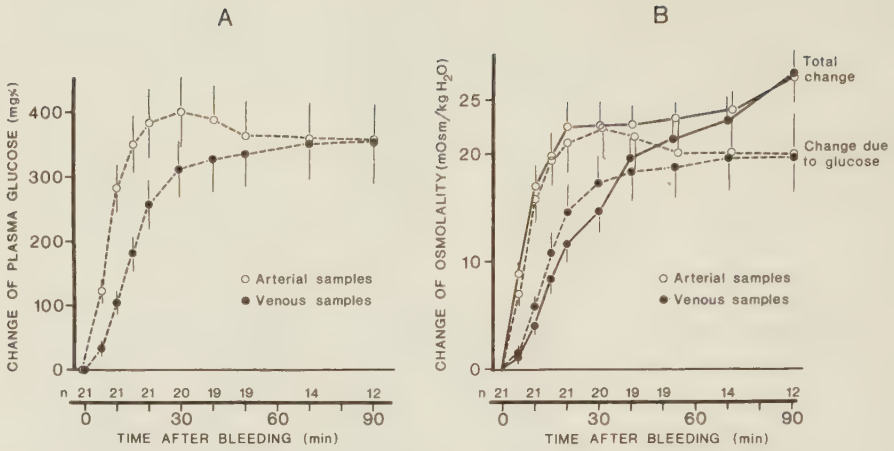

FIG. 3. A. Changes from control value of arterial and popliteal venous plasma glucose concentration in cats bled to 50 mm Hg (n=21). B. Changes above control value of total arterial and venous plasma osmolality in cats bled to 50 mm Hg (n=21) shown together with deduced data for osmolality changes caused by concomitant alteration of plasma glucose concentration. Mean values ±S.E. given.

centrations in the early stage of hemorrhage indicates that glucose entered the extravascular space in this period (cf. Fig. 3, paper II).

Fig. 3 B shows the extent to which the hyperglycemia contributed to the concomitantly observed hyperosmolality in this material. For this deduction, 18 mg% of glucose was considered to correspond to 1 mOsm/kg H_2O. It can be seen that a close correlation indeed existed between the observed changes of osmolality and the values deduced from the changed glucose concentration both in arterial and venous plasma. During the initial 30 min of hemorrhagic hypotension, the hyperglycemia in fact seemed to almost fully account for the plasma hyperosmolality. In later stages of bleeding, however, the observed values for the total osmolality change clearly exceeded those calculated merely from the glucose change, indicating that some other substance(s) contributed to the hyperosmolality at that time.

It should be emphasized here that all data on the glucose content refer to the concentration in plasma (mg/100 ml plasma) and not in whole blood; the latter unit often being used in clinical work. In the control period before bleeding, the plasma glucose level was about 215 mg% in these experiments which corresponds to a blood glucose level of 130 mg%, taking the appropriate hematocrit value into account (and confirmed by direct determinations of the blood glucose level).

Comments

It is a well documented fact that hemorrhage is associated with hyperglycemia. This has been established in several species, including man (for key references see Table II). It may be noted from the data in the table that the magnitude of the hyperglycemia response seems related to the severity of the hemorrhage, a phenomenon which has been analysed in some detail previously (e.g. Robertson 1935). Further, the rate of bleeding appears to influence the magnitude of the hemorrhagic hyperglycemia (Mylon et al. 1944, Carey et al. 1972).

In the present investigation the hemorrhagic hyperglycemia response was confirmed. The study showed, in addition, that the increases of plasma glucose concentration were of such magnitudes as to almost fully account for the concomitantly observed plasma hyperosmolality, especially in early stages of hemorrhagic hypotension (Fig. 3 B). This finding by no means excludes the possibility that there are marked changes also of other plasma constituents during hemorrhage. Thus, previous studies and the present observations have shown that the concentrations of plasma potassium and various nitrogen compounds increase during hemorrhage (cf. D'Silva 1934, Root et al. 1947, Engel 1952; and Table I). The hyperkalemia apparently is due to a loss of intracellular potassium (cf. Hagberg et al. 1967) and may be an effect of acidosis and/or of cell injury caused by impaired circulation.

TABLE II. Maximal increase of blood glucose concentration above the control level in different species during various types of hemorrhage.

Species	Type of hemorrhage (BV = total blood volume before hemorrhage)	Maximal glucose increase (mg%)[x]	Time after bleeding (min)	Investigator(s)
DOG	Bled 33 % of BV	90 (V)	15	Saito et al. 1928
	Bled 70 % of BV	410 (V)	150	Mylon et al. 1944
	Bled 75 % of BV	255 (A)	60	Beatty 1945
	Hypotension at 60 mm Hg	480 (A)[xx]	90	Brooks et al. 1963
	Hypotension at 50 mm Hg	150 (V)	180	Vigas et al. 1972
	Hypotension at 40 mm Hg	460 (A)	180	Chien et al. 1973
	Hypotension at 30 mm Hg	405 (A)	30	Baue et al. 1967
	Hypotension at 30 mm Hg	205 (V)	90	Bauer et al. 1969
CAT	Bled 18 % of BV	60 (A)	15	Brooks 1935
	Bled 32 % of BV	440 (A)	20	Robertson 1935
	Hypotension at 50 mm Hg	400 (A)[xx]	30	Järhult 1973
RABBIT	Bled 20 % of BV	70 (A)	10	Schenk 1894
	Bled 20 % of BV	70 (V)	125	Epstein and Baehr 1914
	Bled 33 % of BV	230 (A)	30	Andersson 1908
RAT	Bled 50 % of BV	75 (?)	300	Engel et al. 1943
SHEEP	Hypotension at 40 mm Hg	125 (A)	75	Halmagyi et al. 1966
PIG	Hypotension at 60 mm Hg	180 (V)	60	Carey and Wallack 1970
MONKEY	Hypotension at 50 mm Hg	90 (V)	120	Hiebert et al. 1973
BABOON	Bled 45 % of BV	180 (V)[xx]	60	Cerchio et al. 1971
	Hypotension at 60 mm Hg	100 (V)	30	Moss et al. 1970
MAN	Bled 15 % of BV	20 (V)	15	Skillman et al. 1971
	(0 mm Hg at admission)	275 (V)	65	Carey et al. 1970

[x] A = arterial samples; V = venous samples

[xx] Plasma glucose concentration

Much of the potassium seems to emanate from the liver, an effect which has been attributed to released adrenaline (Shoemaker et al. 1961, Andersen and Shoemaker 1967, Shoemaker 1968). The observed decrease of the plasma sodium concentration in hemorrhage is an accordance with previous findings (Brooks et al. 1963, Baue et al. 1967) and seems mainly to be the result of an osmotic fluid (water) withdrawal from the intracellular space (see Chapter 6). The chloride, bicarbonate and hydrogen ion concentrations can change significantly in hemorrhage and minor alterations of other constituents might also occur (e.g. Wiggers 1950, Engel 1952, Migone 1962).

All these ionic changes in early hemorrhage seem, however, to virtually cancel each other with regard to the effect on total plasma osmolality. In the present experiments the hyperglycemia was thus, with few exceptions, found to be quite a reliable index of the increase of plasma osmolality.

In later stages (> 60 min) of hemorrhagic hypotension, there was a slow gradual decline of the glucose concentration in face of a maintained hyperosmolality (Fig. 3 B). This decline might be interpreted as an exhaustion of the liver glycogen stores; in fact some authors have reported that animals in hemorrhagic shock may die in a hypoglycemic state (e.g. Engel et al. 1943, Strawitz and Hift 1960, Levenson et al. 1961, Halmagyi et al. 1966). An additional deleterious effect in this phase seems to be marked hyperkalemia. In late stages of hemorrhage, the present results indicate that osmotically active substances from tissues other than the liver may significantly contribute to the maintained hyperosmolality (cf. also Boyd and Mansberger 1968). Such a substance, no doubt, is lactate, which is known to accumulate gradually in plasma during prolonged hemorrhagic hypotension, apparently due to impaired oxygen delivery to the tissues (e.g. Beatty 1945, Nastuk and Beatty 1949, Rosenberg and Rush 1968, Rokkanen et al. 1971, Schweizer and Howland 1972, Chien et al. 1973).

Besides the important hemodynamic effects of the glucose-induced hyper-

osmolality per se (see Chapter 6 and 8), the increased plasma glucose concentration during early hemorrhage seems beneficial insofar that it helps to improve the nutritional situation for the tissues. Such an effect would be of special importance for the brain, the metabolism of which is highly dependant on an adequate glucose supply. The relative need of glucose in over-all cell metabolism might also increase in hemorrhage in view of the fact that the blood concentration of free fatty acids is often reduced after bleeding (e.g. Kovách et al. 1970, Farago et al. 1971, Spitzer and Spitzer 1972).

Chapter 5

ROLES OF THE SYMPATHO-ADRENAL SYSTEM IN HEMORRHAGIC HYPERGLYCEMIA

(Paper IV)

General considerations

Previous studies have demonstrated that the hemorrhagic hyperglycemia is caused by glucose release from the liver. This was proposed as early as 1894 by Schenk, who showed that the hyperglycemia response was abolished by exclusion of the liver from the systemic circulation. Further support for this conclusion was later obtained from direct measurements of the blood glucose concentration in the hepatic vein (e.g. Robertson 1935, Shoemaker et al. 1961, Bashour et al. 1965, Shoemaker et al. 1973). Analyses of the liver glycogen content before and after exsanguination have indicated that the glucose release is mainly due to an increased glycogenolysis (e.g. LePage 1946, Strawitz and Hift 1960).

The stimulus for hepatic glycogenolysis in hemorrhage has commonly been attributed to adrenaline, a hormone known to effectively break down liver glycogen by activation of the adenyl cyclase system (see Sutherland and Rall 1960). Thus, it has been shown that adrenaline secretion is markedly increased and that the plasma adrenaline level may rise up to 90 times the control value during hemorrhage (e.g. Bedford 1917, Saito et al. 1928, Watts 1956, Manger et al. 1957, Walker et al. 1959, Walton et al. 1959, Rosenberg et al. 1961, Hall and Hodge 1971, Carey et al. 1972). The concept of a dominant role of adrenaline in the hyperglycemia response has been strengthened by the finding that adrenalectomy can cause a decrease or abolition of the hemorrhagic hyperglycemia (e.g. Engel et al. 1943, Halmagyi et al. 1967, McCormick et al. 1969), an effect present also after substitution of glucocorticoids (Hiebert et al. 1973).

During the course of the present work we observed, however, that a hemorrhagic hyperglycemia was still present after bilateral removal of the adrenal glands, suggesting a multifactorial control of the glucose release. Indirect support for this hypothesis was also obtained from some recent studies showing an increased plasma glucose concentration during stimulation of the splanchnic nerves in adrenalectomized animals (Edwards 1972a, Edwards and Silver 1972, Bloom et al. 1973b). In the series of experiments to be described, an attempt was made to define possible different links of the sympatho-adrenal system involved in the hemorrhagic hyperglycemia response.

Present results

The role of the liver in the hyperglycemia response during hemorrhagic hypotension (50 mm Hg) was first to be established. For this purpose, determinations of glucose were made in blood sampled simultaneously from the carotid artery and from two sites in the caval vein, i.e. at the entrance of the hepatic vein ('hepatic' vein) and at the iliac bifurcation. Some samples were also taken from the portal and renal veins. The analyses revealed that the plasma glucose concentration in the 'hepatic' vein exceeded that in the arterial blood which, in turn, exceeded that in the iliac and portal veins (Paper IV, see Fig. 2). The glucose level was higher in samples taken from the renal than from the iliac vein, but lower than the level in 'hepatic' venous blood. The conclusion was therefore reached that the increased plasma glucose concentration in the present type of hemorrhage experiments is due to release of this substance from the liver, in agreement with findings in other hemorrhagic situations (see ref. above).

An attempt was then made to investigate whether the hemorrhagic hyperglycemia could be attributed to hormone release from the adrenals, to a sympathetic nervous influence on the liver, and/or to a adrenergically in-

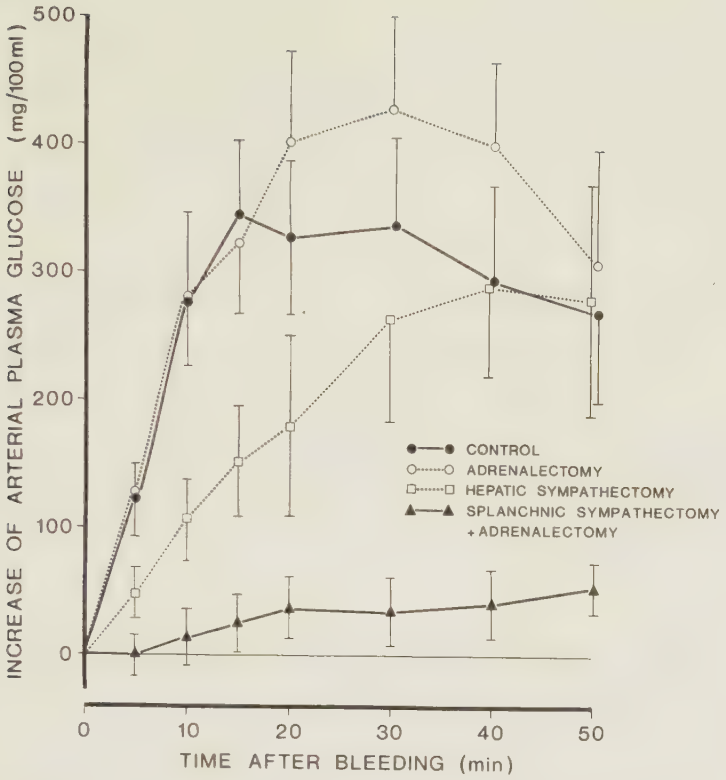

FIG. 4. Increases of arterial plasma glucose concentration above the control level during hemorrhagic hypotension at 50 mm Hg in control animals (n=14), animals with adrenalectomy (n=7), animals with regional hepatic sympathectomy (n=6), and animals with splanchnic sympathectomy combined with adrenalectomy (n=6). Mean values ±S.E. are given.

duced release of glucagon from the pancreas. The hyperglycemia response was therefore analysed in animals with an intact sympatho-adrenal system and compared with the response after adrenalectomy, after regional hepatic sympathectomy, and after splanchnic sympahtectomy combined with adrenalectomy. In addition, the level of glucagon in the portal venous blood was determined.

Fig. 4 (reproduced from paper IV) shows that the arterial plasma glucose

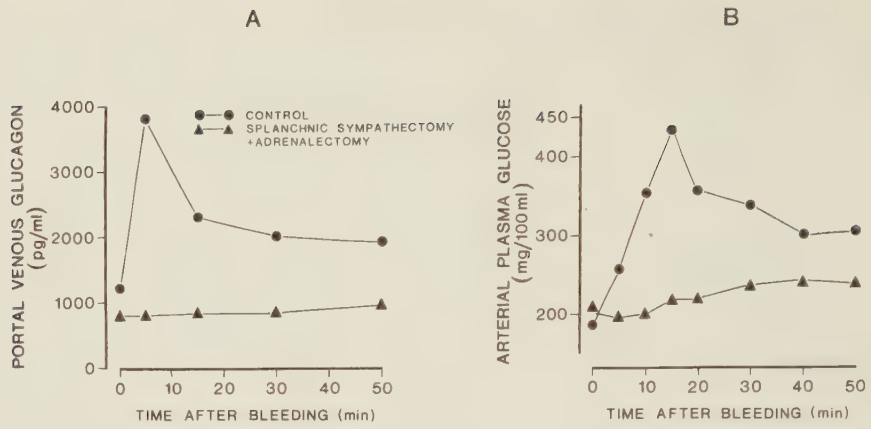

FIG. 5. Mean values for portal venous glucagon concentration (panel A) and for arterial plasma glucose concentration (panel B) during hemorrhagic hypotension at 50 mm Hg in 2 cats with an intact sympatho-adrenal system and in 2 cats with splanchnic sympathectomy + adrenalectomy.

concentration rose rapidly during hemorrhagic hypotension at 50 mm Hg both in the cats with an intact sympatho-adrenal system and in the adrenalectomized animals. When the hepatic nerves were sectioned, the hyperglycemia response was depressed but only in the early phases of hypotension (< 30 min). However, when the splanchnic nerves were cut bilaterally in adrenalectomized cats, the response virtually vanished.

The level of immuno-reactive glucagon in portal venous plasma was determined in 2 cats with an intact sympatho-adrenal system and in 2 cats after adrenalectomy and bilateral splanchnic denervation. In the intact animals, hemorrhage caused an almost instantaneous rise of portal venous glucagon concentration, whereas no such increase was observed after bilateral splanchnic denervation in adrenalectomized cats (Fig. 5 A, reproduced from paper IV). The concomitant arterial glucose concentrations are depicted in Fig. 5 B, showing marked differences between the two groups of animal.

Comments

The present results confirm the opinion that the hemorrhagic hyperglycemia is mainly due to glucose release from the liver. Taken together with previous reports, they also indicate that this hepatic glucose release is mediated by at least three different mechanisms: a. via a direct sympathetic nerve influence on the liver; b. via an adrenergic release of glucagon from the pancreas; and c. via a release of catecholamines from the adrenal glands. The study further suggests that these mechanisms quite effectively can compensate for each other; thus after removal of one link, a marked hemorrhagic hyperglycemia response was still present. The hyperglycemia, as will be discussed below, cannot be attributed to a decreased insulin secretion.

Although, as mentioned above, most previous investigators have suggested adrenaline to be the sole cause of the glucose release in bleeding, there are some earlier studies which support the proposed multifactorial hypothesis. Thus, Mylon et al. (1944) reported that the hyperglycemia evoked by infusion of large doses of adrenaline into non-bled animals was "mild" compared to that seen in hemorrhage, and Carey et al. (1972) arrived at the same conclusion. The splanchnic nerve stimulation experiments performed by Edwards group (see above) can also be taken as indirect evidence for the multifactorial hypothesis.

Some details concerning the different links of the sympatho-adrenal system in the hyperglycemia response will be considered.

Sympathetic nerve influence on the liver. In the present hemorrhage experiments, the glucose level rose by 400 mg% in adrenalectomized animals and the response was depressed after sectioning of the hepatic nerves. These data suggest a direct adrenergic nervous influence on the hepatic glucose release in bleeding, an opinion indirectly corroborated by the following previous observations: Strong excitation of the hepatic nerves (20 Hz) in

adrenalectomized cats leads to an increase of the arterial glucose level by about 200 mg% (Edwards 1972b). Stimulation of the hepatic nerves causes an abrupt rise in the activity of several enzymes involved in liver glycogenolysis (Shimazu and Amakawa 1968a,b). Further, recent histochemical studies reveal a rich direct adrenergic innervation of the liver parenchymal cells, at least in humans (Nobin et al., unpublished).

Adrenergic glucagon release. The fact that the concentration of portal venous glucagon rapidly increased after bleeding in intact animals, but remained unchanged in adrenalectomized animals with severed splanchnic nerves, strongly indicates that glucagon was released via the sympatho-adrenal system. An analogous conclusion was made by Bloom et al. (1973a), who found that glucagon could be released in the monkey in response to other types of stress. Further, direct excitation of the sympathetic nerves to the pancreas in cats and calves has been shown to cause a rapid glucagon liberation (Esterhuizen and Howell 1970, Bloom et al. 1973b). In the latter study, a close co-ordination in time was found to exist between the increase in glucagon and the subsequent increment of the arterial plasma glucose concentration. The magnitude of this plasma glucose rise amounted to about 100 mg% when the sympathetic nerves were strongly activated. In the present hemorrhage experiments, a clearcut glucose increase occurred during the peak glucagon level, but the maximum glucose rise was obtained later, apparently due to additional influence from the other control systems. The data taken together indicate that adrenergically induced release of glucagon is involved in the hemorrhagic hyperglycemia response, although the quantitative role of this mechanism might be relatively subordinate in comparison to the others. Some observations suggest that glucagon is released also in the late stages of hemorrhage, but then as a result of the concomitant hypoglycemia (Halmagyi et al. 1969).

Cathecholamine release from the adrenals. As stated above, numerous in-

vestigations have demonstrated convincingly that adrenaline and noradrenaline are released from the adrenals in large amounts during hemorrhage contributing to the hyperglycemia response. A detailed study of this mechanism was therefore not considered essential for the present analysis. Our results of a well maintained hyperglycemia after adrenalectomy might at first sight seem to contradict this concept, but in all probability can be explained by an effective compensation via the other regulatory mechanisms. A significant contribution of the adrenal medullary hormones to the glucose rise in our experiments in fact seemed established by the results obtained in animals with cut hepatic nerves. Under these circumstances, hemorrhage evoked an arterial hyperglycemia of about 300 mg% above control, but according to the findings of Bloom et al. (1973b), such large a glucose increase cannot possibly be attributed to the glucagon mechanism alone.

Mention should be made here that the hemorrhagic hyperglycemia (and hyperosmolality) response in animals with an intact sympatho-adrenal system was almost totally abolished after α-adrenergic blockade with phenoxybenzamine (5-10 mg/kg) but not after β-adrenergic blockade with propranolol (1 mg/kg). Halmagyi et al. (1968) made quite similar observations in the sheep; propranolol pretreatment did not change the hemorrhagic hyperglycemia response, whereas phenoxybenzamine (1 mg/kg) depressed the response. These findings suggest that the liver glucose release during hemorrhage, at least in the cat and the sheep, mainly is mediated via α-adrenoceptors (cf. Himms-Hagen 1967, Hornbrook 1970).

The present study thus indicates that there are three (main) links of the sympatho-adrenal system which together contribute to the elicitation of the hemorrhagic hyperglycemia response. This does not rule out the possibility that other control mechanisms can be involved as well, for instance via release of growth hormone (Meyer and Knobil 1967, Carey et al. 1971, Skillman et al. 1971) and/or glucocorticoids (e.g. Sayers et al. 1945,

Johnson et al. 1971, Cryer and Gann 1974). Since, in the present experiments, the hyperglycemia was virtually abolished when the splanchnic nerves were cut in adrenalectomized cats, the effect of the mentioned hormones on the hyperglycemic response must have been quite small in this particular type of hemorrhage.

The hyperglycemia response does, however, not seem to depend upon a hypothetical decrease of the insulin secretion to judge from previous studies. Thus, the insulin level is reported to be somewhat increased during bleeding in dogs (e.g. McCormick et al. 1967, Vigas et al. 1972) and virtually unchanged in primates, including man (e.g. Carey et al. 1970, Moss et al. 1970, Cerchio et al. 1971, Hiebert et al. 1973). The lack of insulin release in response to hemorrhagic hyperglycemia has been attributed to an inhibitory effect of the sympatho-adrenal system (e.g. Hiebert et al. 1973; cf. also Malaisse et al. 1967, Porte et al. 1967, Bloom et al. 1973b).

It is quite likely that the hemorrhagic hyperglycemia (and hyperosmolality) response, induced via the different links of the sympatho-adrenal system, is reflexly controlled by cardiovascular receptors. The nature of such a receptor mechanism remains to be elucidated. In some preliminary experiments we observed, however, that the hyperglycemia and hyperosmolality responses were more closely correlated to the induced decrease of arterial blood pressure than to the magnitude of the shed blood volume. This finding might be taken to indicate that the response is governed mainly by the arterial mechanoreceptors.

Chapter 6

OSMOTIC FLUID TRANSFER FROM TISSUES TO BLOOD DURING HEMORRHAGIC HYPOTENSION (Paper I-III)

General considerations

It was suggested long ago that extravascular fluid enters the circulatory system after a blood loss. This hypothesis was based on observations showing that the concentration of hemoglobin and/or red blood cells was lowered after hemorrhage (e.g. Vierordt 1854, Bierfreund 1891, Koeppe 1895), a hemodilution which seemed to occur mainly in the initial posthemorrhagic period (Boycott and Douglas 1909, Hirota 1928). The phenomenon of a partial plasma volume restoration after bleeding has been confirmed and quantitatively defined in more detail by later studies using different techniques for plasma volume determination. These investigations on animals have revealed that the main fluid replacement occurs within the first hour after bleeding (for ref. see Chien 1967; see also Boyd and Mansberger 1968, Carey 1973, Chien et al. 1973) and similar conclusions have been reached also from experiments in humans (e.g. Ebert et al. 1941, Kaufmann and Müller 1958, Skillman et al. 1967 a).

The mechanism for this hemodynamically important transcapillary absorption of extravascular fluid after hemorrhage was for a long time attributed solely to a passive fall of capillary hydrostatic pressure, secondary to the decline of arterial and venous blood pressure. However, some indications that the sympathetic nervous system might be involved in the process were obtained by Chien (1958). He found that sympathectomy clearly diminished the hemodilution after hemorrhage and that an absorption of extravascular fluid to the blood stream occurred also after bleedings too small to cause significant changes in arterial or venous pressure.

Direct experimental evidence for a net transcapillary absorption of extravascular fluid in response to activation of the sympathetic vasoconstrictor nerves was first presented by Mellander (1960) on a skeletal muscle and skin region in the cat. He also showed that the phenomenon was due to a resetting of the pre-/postcapillary resistance ratio, in turn causing a decrease of the capillary hydrostatic pressure. Similar effects of sympathetic nerve stimulation on net transcapillary fluid exchange were observed during regional and hemorrhagic hypotension; the rate of absorption, however, decreased with time due to impaired reactivity of the precapillary resistance vessels (Lewis and Mellander 1962, Mellander and Lewis 1963). The cardiovascular receptor control of the sympathetically mediated net capillary fluid transfer was investigated in detail by Öberg (1964). Small to moderate hemorrhage of 5-15 min duration consistently caused an augmented vasoconstrictor fibre discharge, which led to mobilization of extravascular fluid to the blood stream. Such an "autotransfusion" was present in skeletal muscle and skin, but did not occur in the small intestine. The effect was quantitatively most pronounced in muscle tissue and was clearly detectable even after minor blood losses. Öberg also demonstrated that this reflex fluid redistribution was goverened by arterial mechano- and chemoreceptors, and later studies indicate that the low pressure receptors might be involved as well (e.g. Öberg and White 1970). Similar studies during more prolonged periods of moderate hemorrhage showed that a fluid absorption from skeletal muscle occurred during the first 25 min, and at a maximum rate of 0.1 ml/min x 100 g tissue after 5 min (Lundgren et al. 1964). These results have later been confirmed in essential parts by Haddy's group (e.g. Haddy et al. 1965, Schwinghamer et al. 1970, Grega et al. 1971). Reflexly induced mobilization of extravascular fluid from muscle tissue has also been demonstrated in humans after a 10 % decrease of the circulating blood volume (Mellander and Öberg 1967).

Capillary fluid transfer from the extravascular to the intravascular compartment can be accomplished by mechanisms other than those implicit in the Starling concept. Hyperosmolality of non-protein origin has thus been shown to cause a pronounced transcapillary fluid redistribution during heavy exercise both in animals and man (Lundvall 1972, Lundvall et al. 1972). Since, in early hemorrhage, the tissues are perfused with blood that is hyperosmolar compared to the extravascular fluid (Chapter 3), a prerequisite exists for an analogous osmotic transcapillary fluid absorption. Experiments were therefore designed to reveal such possible fluid transfer in different tissues during bleeding. The analysis indicated that this mechanism indeed is present and participates in the plasma volume control during hemorrhagic hypotension.

Present results

To be able to reveal possible osmotic capillary fluid transfer in hemorrhage, the influences of sympatho-adrenal reflex mechanisms and of alterations of arterial and venous pressure on capillary fluid exchange must be eliminated. In the experiments designed for such an analysis, reflex effects were excluded by surgical and pharmacological sympathectomy and regional venous outflow pressure was kept constant. The influence of the arterial pressure fall per se on the exchange process will be considered separately (Chapter 7). Observations of the capillary fluid transfer under these conditions were made during hemorrhagic hypotension in three different tissues, viz. skeletal muscle, skin, and intestine.

Skeletal muscle. Fig. 6 (reproduced from paper II) shows the collected data for the arterio-venous osmolar difference, net transcapillary fluid movement, and regional blood flow in the sympathectomized and α-blocked cat skeletal muscle region during 90 min of hemorrhagic hypotension at 50 mm Hg. For comparison, corresponding data from an intact muscle region are shown

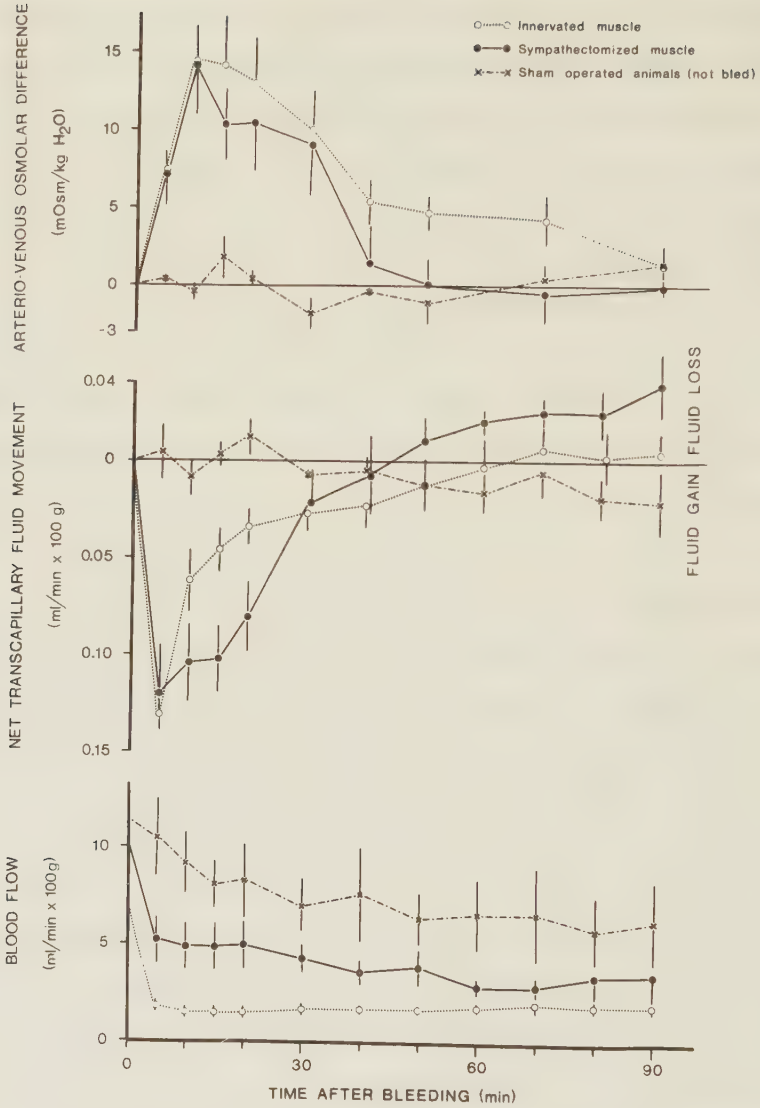

FIG. 6. Arterio-venous osmolar difference, net transcapillary fluid movement, and regional blood flow in an innervated (n=13) and a sympathectomized (n=14) skeletal muscle region of cats subjected to hemorrhagic hypotension (50 mm Hg) and in sham operated cats (n=4). Data expressed as mean values ±S.E.

as well as observations from 4 sham operated animals.

In the sympathectomized muscle region (Fig. 6, solid lines), a net transcapillary fluid absorption occurred as long as the arterio-venous osmolar difference was positive, i.e. for about 40 min. The fluid absorption was most pronounced during the initial 20 min of hypotension, and the close coordination in time with the positive arterio-venous osmolar difference (reflecting the transcapillary osmolar gradient) indicates that the absorption was due to osmosis (for detailed discussion see below). In the late stages of hemorrhagic hypotension (> 50 min), a moderate transcapillary fluid filtration was observed. The regional blood flow (lower panel) decreased roughly in proportion to the lowered perfusion pressure; if anything, vascular resistance was somewhat reduced in the initial phase (during absorption) and slightly increased in the late phase of hypotension (during filtration).

The net transcapillary fluid absorption in the intact skeletal muscle region during hemorrhagic hypotension at 50 mm Hg (Fig. 6, dotted lines) occurred at a somewhat slower rate in certain periods (10-20 min) than in the sympathectomized region, despite the fact that the arterio-venous osmolar difference (upper panel) was quite similar in the two types of experiment. This was a somewhat surprising result since it was expected that the reflex mechanism for fluid absorption, operating in the intact region, would add to the described osmotic fluid absorption. Recent studies by Lundvall (1972) indicate, however, that the osmotic fluid flux in skeletal muscle is directly dependent both on the arterio-venous osmolar gradient and on the magnitude of the regional blood flow. Thus, for a given arterio-venous osmolar gradient, an increase of the regional blood flow by 100 per cent was shown to lead to a corresponding increase of the osmotic fluid transfer. This finding is relevant for the present analysis, since sympathectomy clearly augmented the regional blood flow (Fig. 6, lower panel). Hence, the data for osmotic fluid absorption (solid line) might be an overestimation of what actually occurs in the intact muscle.

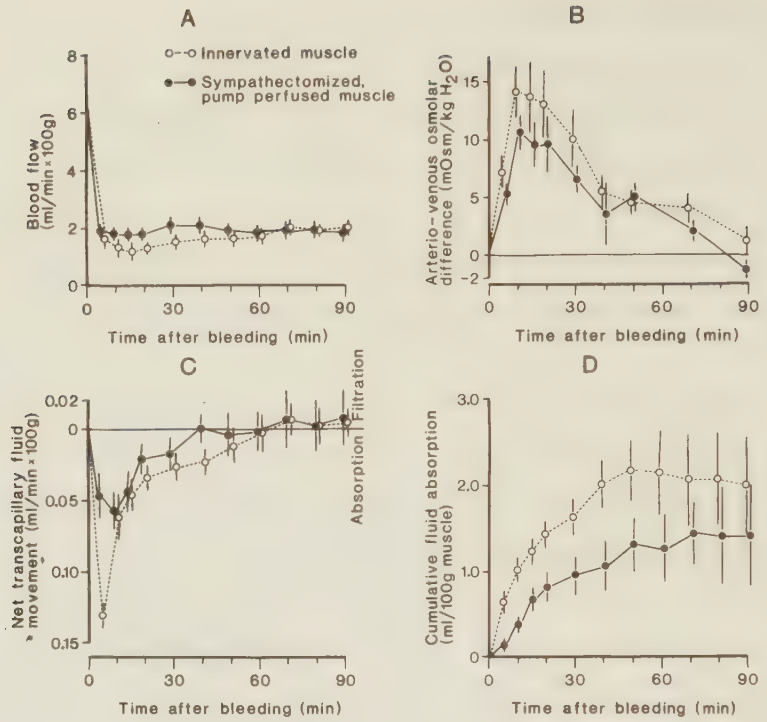

FIG. 7. Comparative data in hemorrhage for arterio-venous osmolar difference (panel B), net transcapillary fluid movement (panel C), and cumulative fluid absorption from the extravascular space (panel D) in the innervated (n=13) and sympathectomized (n=9) muscle region, when blood flow in the latter region was mechanically adjusted to about the same level as occurred in the innervated one (panel A). Data for innervated muscle (panel A-C) same as in Fig. 6. Mean values ±S.E. given.

This problem was approached in some experiments (Fig. 7, reproduced from paper II), in which the transcapillary fluid absorption during hemorrhage was determined in the sympathectomized muscle, when regional blood flow was adjusted by a perfusion pump to the same level as in the intact region (panel A). Since the arterio-venous osmolar difference in such a pump-perfused sympathectomized region was similar to that in the intact muscle region (panel B), the observed net transcapillary fluid transfer in the former was

considered to represent, in approximate terms, the "true" osmotic absorption of extravascular fluid in skeletal muscle during hemorrhagic hypotension of this type. The net fluid absorption in the sympathectomized region was clearly diminished by the blood flow reduction (compare Fig. 6 and Fig. 7 C) and was now smaller than in the intact muscle (Fig. 7 C). - The analysis performed in Chapter 7 shows that this fluid absorption cannot be attributed to the low arterial inflow pressure per se (30-40 mm Hg) prevailing in the sympathectomized pump perfused tissue.

The cumulative transcapillary fluid absorption in skeletal muscle during hemorrhagic hypotension is depicted in Fig. 7 D, in which the dotted curve represents total absorption and the solid curve the fraction caused by osmosis alone (derived from the absorption data in the sympathectomized pump perfused region). After 10 min of hypotension, the total amount of absorbed extravascular fluid was 1.0 ml/100 g muscle ($\approx$ 35 % osmotic), after 20 min 1.4 ml/100 g ($\approx$ 55 % osmotic), and after 60 min 2.1 ml/100 g ($\approx$ 60 % osmotic). It might be concluded that the adrenergic reflex and the osmotic mechanisms both are important for the plasma volume restoration after hemorrhage, and that the reflex mechanism, at least in the present type of bleeding, is dominant in the early ($<$ 20 min) stage of hypotension.

In an attempt to further support the concept of an osmotic transcapillary fluid absorption in hemorrhage, the following type of experiment was performed: The osmolality of the blood was increased in non-bled, adrenalectomized animals (n=5) by slow intravenous infusions of hypertonic glucose solution so as to create an arterial hyperosmolality of similar nature and magnitude to that in the hemorrhage experiments. The blood flow in the sympathectomized muscle region was mechanically adjusted to the same average levels as in the bleeding experiments (cf. Fig. 6 and 7). The rates of fluid absorption resulting from such infusions were found to agree closely with the absorption rates depicted by the solid lines in Fig. 6 and 7 C, espe-

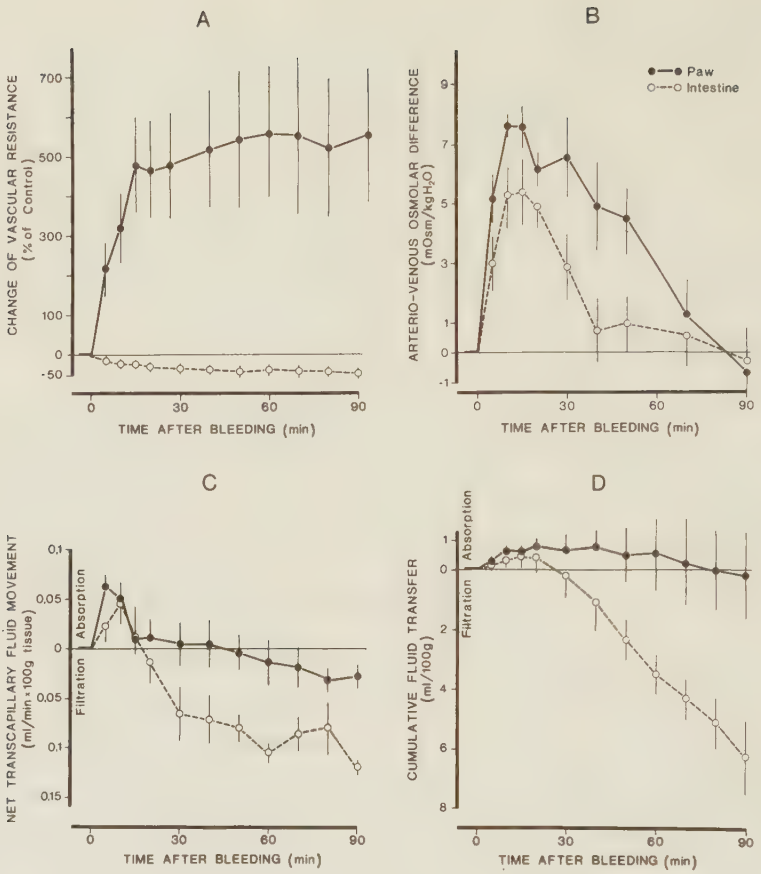

FIG. 8. Circulatory events in the sympathectomized α-blocked paw (●——●, 8 expts) and small intestine (o----o, 8 expts) during hemorrhagic hypotension at 50 mm Hg in the cat. Panel A shows the change of vascular resistance, panel B the arterio-venous osmolar difference, panel C the net transcapillary fluid movement, and panel D the cumulative capillary fluid transfer. Mean values ±S.E. are given.

cially in the early stage of bleeding.

Skin. The changes of plasma osmolality in arterial and cutaneous venous blood revealed the existance of a positive transcapillary osmolar gradient in the sympathectomized and α-blocked paw during the first hour of hemorrhagic hypotension at 50 mm Hg (Fig. 8 B, reproduced from paper III). The

gradient was somewhat lower than in the skeletal muscle due to a less pronounced arterial hyperosmolality in these particular experiments. Observations of net transcapillary fluid movement showed that a moderate absorption of extravascular fluid occurred in the initial period of hypotension (Fig. 8 C), when the arterio-venous osmolar difference was most pronounced. Late in hemorrhage a slight fluid filtration was present. The cumulative fluid transfer in the paw during hemorrhagic hypotension is depicted in Fig. 8 D. After 40 min, a total of 0.8 ml of extravascular fluid per 100 g tissue had been transferred to the circulatory system, but this fluid volume was returned to the tissue after 80 min of hypotension due to gradually developing filtration. - The vascular resistance in the sympathectomized paw increased markedly during the hypotension (Fig. 8 A), most likely due to passive factors, as evidenced by regional hypotension experiments (see Chapter 7). It was concluded that the fluid absorption in early hemorrhage was due to osmosis, an opinion supported by hypertonic infusion experiments similar to those described for skeletal muscle.

Intestine. Hemorrhagic hypotension at 50 mm Hg evoked only a moderate increase of the arterio-venous osmolar difference in the small intestine (Fig. 8 B) compared to that in skeletal muscle; this difference was mainly due to a more rapid increase of the venous osmolality in the intestine. The net transcapillary absorption in the α-blocked intestine was a transient phenomenon (Fig. 8 C) and the most prominent observation, in fact, was a marked fluid filtration in late stages of hypotension. This filtration apparently was due to increased capillary hydrostatic pressure related to the gradual decline of vascular resistance (Fig. 8 A). As can be seen from panel D, the cumulative fluid absorption from the intestine was quite small and the main effect was a net loss of plasma fluid, amounting to some 6 ml/100 g tissue after 90 min. - From these observations the conclusion was reached that the hemorrhagic hyperosmolality caused only a slight transient

fluid absorption from the intestine.

Comments

Data on net transcapillary fluid movement in skeletal muscle, skin, and intestine were derived from plethysmographically recorded changes of tissue volume during constant arterial inflow pressure and venous outflow pressure. Lymph drainage from the regions was effectively prevented by careful cauterization and ligation. Under these conditions a change of tissue volume can represent two events, viz. a net transcapillary fluid movement and/or an altered regional blood volume (capacitance response). Critical analyses of volume changes recorded with this technique (Mellander 1960, Öberg 1964, 1967) have shown that net transcapillary fluid movements can be readily distinguished from capacitance responses, an interpretation which has been validated by concomitant use of the ^{51}Cr-method for separate determination of changes of regional blood volume (e.g. Åblad and Mellander 1963, Kjellmer 1965). These analyses have further shown that the capacitance responses almost invariably are closely co-ordinated in time with reactions within the resistance vessels.

The main interest in the present study was focused on net transcapillary fluid absorption and such an effect was found to occur within the first 40 min of hemorrhagic hypotension. The observations of fluid absorption were made after the arterial pressure had reached a steady level of 50 mm Hg (which was accomplished in less than 3 min after the start of the bleeding) and in a state of reasonably stable tone of the resistance and, hence, of the capacitance vessels. In some individual experiments, abrupt minor changes of vascular resistance did occur, but, then, the concomitant capacitance effects were of course disregarded in the analysis of the transcapillary fluid movement. It is therefore concluded that the present approach permitted quite an accurate quantitative evaluation of the transcapillary fluid

absorption in the early stage of bleeding. - In the later stages, where fluid filtration appeared, the analysis might be somewhat less accurate, since, in this period, more gradual minor changes of vascular resistance (and perhaps therfore also of vascular capacitance) were present. The inherent error seems to be small, however, and, possibly, cannot alter the main conclusions drawn.

The transcapillary fluid absorption process is of hemodynamic importance for the replacement of plasma volume in hemorrhage. Such fluid absorption occurs in skeletal muscle, skin, and intestine, but is of major quantitative significance only in muscle due to its very large tissue mass. The main emphasis was therefore placed on the events in this tissue and the mechanisms for the fluid absorption will be considered first.

The study revealed that fluid was mobilized from the extravascular space of skeletal muscle, both when the sympatho-adrenal system was intact and after regional α-adrenergic blockade and sympathectomy. Earlier studies (see above) have clearly shown that an adrenergic resetting of the pre-/postcapillary resistance ratio occurs in hemorrhage, leading to decreased capillary hydrostatic pressure and, hence, to fluid absorption in the intact muscle. It follows that, in the α-blocked region, some other mechanism(s) must have been responsible for the observed fluid absorption and we propose that it is due to osmosis caused by agents other than the plasma proteins. This hypothesis is based on the following findings: a. The hemorrhagic hypotension was associated with a pronounced increase of arterial plasma osmolality (Chapter 3); b. This hyperosmolality was mainly due to release of glucose from the liver and, hence, it primarily developed in the blood stream (Chapter 4 and 5); c. In the period of fluid absorption, a clearcut arterio-venous osmolar difference existed in the tissue, in turn implying the presence of a concomitant transcapillary osmolar gradient; d. The magnitude and time course of the transcapillary fluid absorption we-

re closely related to those of the arterio-venous osmolar difference; e. Graded arterial hyperosmolality, produced by slow i.v. infusions of glucose in non-bled animals, evoked fluid absorptions in the α-blocked muscle region of similar magnitudes to those observed in hemorrhage.

It might be argued that the fall of arterial pressure per se during hemorrhage would lower the capillary hydrostatic pressure and cause fluid absorption. This possibility was refuted by the regional hypotension experiments to be described in Chapter 7, which showed that no significant transcapillary fluid absorption was evoked when arterial inflow pressure to the muscle region was mechanically adjusted to 50 mm Hg. The maintenance of capillary pressure in this situation was mainly explained by autoregulatory adjustments of vascular tone.

Several studies have shown that renin-angiotensin and vasopressin can be released during hemorrhage (e.g. Dexter et al. 1943, Ginsburg and Heller 1953, Weinstein et al. 1960, Skillman et al. 1967b, Share 1968, Rocha e Silva and Rosenberg 1969, McNeil et al. 1970, Hall and Hodge 1971, Errington and Rocha e Silva 1972). Hypothetically, these vasoconstrictors might have influenced vascular tone so as to cause transcapillary fluid absorption. However, direct studies of capillary fluid exchange in skeletal muscle during angiotensin infusion have shown that this agent does not cause any significant fluid transfer (Folkow et al. 1961, Järhult 1971) and this seems to be true also with regard to vasopressin (Diana et al. 1967). Further, there were no signs of significant release of such vasoconstrictor agents in the present hypotension experiments, since vascular resistance in the α-blocked muscle and intestine in fact was decreased during the period of fluid absorption (Fig. 6 and 8).

We therefore conclude that the transcapillary absorption of extravascular fluid from muscle tissue to the blood stream during hemorrhagic hypotension at 50 mm Hg to a significant extent is caused by an osmotic process

mainly related to the plasma hyperglycemia. The experiments also indicate that the same mechanism is operating in skin and intestine, although the osmotic fluid absorption in these tissues is quantitatively less pronounced than in skeletal muscle.

The question then arises from which tissue compartment the absorbed extravascular fluid emanates. The released glucose molecules, responsible for the hemorrhagic hyperosmolality, will primarily be distributed in the blood stream, but secondarily enter the interstitium and increase its osmolality as well. Such an interstitial hyperosmolality must lead to significant osmotic fluid (water) withdrawal from the intracellular space, since the reflection coefficient of the cell membranes for glucose can be considered to be close to unity and since the glucose transport into most cells is a slow process.

Experimental support for such a fluid redistribution was obtained from the observed decrease of plasma sodium concentration after bleeding (Chapter 4), indicating a dilution, and a relative expansion, of the entire extracellular space. This opinion is also in agreement with some direct studies of the extracellular fluid volume in early hemorrhage (e.g. Appelgren 1972). In fact, the osmolar control system in hemorrhage might therefore basically be aimed at a restoration of the extracellular fluid volume, but, due to the time sequence of the hyperosmolar events, it will also institute a fluid redistribution within this space from the interstitial into the intravascular compartment.

Such an osmotic absorption process can be expected to be more effective across capillaries with continuous than with fenestrated endothelium due to the lower solute permeability in the former type (cf. Landis and Pappenheimer 1963). The experimental observations also demonstrated such a difference with a more pronounced osmotic absorption in skeletal muscle than in intestine. Even in muscle capillaries, however, the reflection coefficient

for glucose is far below unity (perhaps in the range of 0.2-0.3, cf. Perl 1971), but evidently high enough to create opportunities for glucose-osmotic net fluid movement. Yet, the effective driving force for osmotic fluid movement of course is much smaller than what would be predicted from van't Hoff's law. A rough estimate of this driving force (mm Hg) was obtained by dividing the observed rate of osmotic fluid absorption by the capillary filtration coefficient. Such calculations indicated that the mean osmotic driving force during hemorrhage never exceeded 7 mm Hg in the α-blocked skeletal muscle. The magnitude of the true transcapillary osmolar gradient cannot be exactly defined in these experiments, but, for a given average capillary flow velocity, it is related to the arterio-venous osmolar difference (for details see Lundvall 1972). At the relatively low flow states prevailing in the muscle during hemorrhage, the venous osmolality would be quite representative for interstitial osmolality, but the mean transcapillary osmolar gradient of course is considerably smaller than the arterio-venous osmolar difference. Thus, if the reflection coefficient is assumed to be 0.25, and the transcapillary glucose-osmotic effective driving force is 7 mm Hg (see above), the value for the mean transcapillary osmolar gradient can be estimated to be about 2 mOsm/kg H_2O.

The present study has shown that hemorrhagic hypotension at 50 mm Hg is associated with considerable transcapillary absorption of extravascular fluid to the blood stream, an event most pronounced in skeletal muscle. In the intact organism, this fluid absorption is accomplished by two mechanisms, i.e. by the discussed osmolar control and by a reflex adrenergic control (cf. Öberg 1964) which lowers capillary hydrostatic pressure via a resetting of the pre-/postcapillary resistance ratio. Quantitative data for these two processes in cat muscle tissue were given in Fig. 7 D.

Some aspects of the hemodynamic significance of the hemorrhagic fluid absorption will be considered below, and might be most readily appreciated

by making an extrapolation of the present data from the cat to man. Such an extrapolation seems to be justified for the following reasons: Reflex fluid absorption from muscle and skin has been demonstrated to occur in the human being after reduction of the circulating blood volume (Mellander and Öberg 1967) and at similar rates to those in the cat, taking the induced hypovolemia into account. Further, severe hemorrhage in man is known to evoke an arterial hyperosmolality and hyperglycemia of similar magnitudes to those reported here for the cat (Boyd and Mansberger 1968, Boyd et al. 1970, Carey et al. 1970). From the data given in Fig. 7 D, it may then be estimated that hemorrhagic hypotension at a level of 50 mm Hg would cause a total reflex fluid absorption of about 250 ml and a total osmotic fluid absorption of about 400 ml from all human skeletal muscles (30 kg) within the first hour of bleeding. The entire fluid absorption from the human muscles accomplished by both mechanisms would thus comprise some 650 ml within this relatively short period of time, a figure compatible with data derived from determinations of the hemodilution after comparable bleeding in man (Kaufmann and Müller 1958).

These considerations indicate that transcapillary fluid absorption in skeletal muscle constitutes a hemodynamically important principle for the plasma volume restoration in hemorrhage and that the osmolar control can be at least as effective as the reflex adrenergic regulation. However, the reflex mechanism is involved already at minor blood losses (cf. Öberg 1964), whereas the osmotic mechanism seems to be put into play first when the bleeding is more pronounced.

Osmotic fluid absorption was shown to occur also in skin and intestine (Fig. 8 D), but these events contribute little to the overall plasma volume regulation. Thus, extrapolation of the data to the whole skin and intestinal tissues in man (each about 2 kg) indicates that the total osmotic fluid withdrawal from skin would comprise only some 20 ml and from intestine some

10 ml in severe hemorrhage.

The absorbed extravascular fluid is protein-poor and leads to a decrease of the plasma colloid-osmotic pressure. Yet, the absorbed fluid volume is retained within the circulatory system for considerable length of time, as evidenced for instance by a maintained hemodilution (e.g. Carey 1973, Chien et al. 1973). There has been no satisfactory explanation of this phenomenon, but it appears that it can be understood in view of the described osmolar fluid control. Thus, when intracellular water is osmotically absorbed into the interstitial space, a dilution of the colloids in the interstitium of all tissues ensues and, hence, the interstitial colloid-osmotic pressure decreases. Such an effect would tend to counterbalance the influence of a decreased plasma protein concentration on the Starling transcapillary fluid equilibrium in the body. The efficiency of this mechanism increases if the interstitial protein concentration is high before dilution. Recent studies have indicated that interstitial colloid-osmotic pressure indeed is significant and much higher than previously assumed (for ref. see Aukland 1973 and Lönsmann Poulsen 1974).

The discussed compensatory mechanisms for plasma volume restoration in the present type of bleeding seem to be operating predominantly in the first hour of hemorrhagic hypotension. In later stages, however, a transcapillary fluid loss was observed in all three tissues (Fig. 6 and 8), particularly pronounced in the intestine. Such a fluid filtration has been observed in skeletal muscle and skin in some previous studies (e.g. Lundgren et al. 1964, Hollenberg and Nickerson 1970) and is well established phenomenon in the gut during hemorrhage (e.g. Johnson and Selkurt 1958, Glenert and Pedersen 1967, Cook et al. 1971, Haglund 1973). This fluid loss occurred when the arterio-venous osmolar gradient had vanished and at a time when the neurogenically induced fluid absorption has been reported to be insignificant (Mellander and Lewis 1963). A similar fluid loss was also observed

after prolonged periods of regional hypotension (Chapter 7). It is suggested that this plasma fluid escape was caused mainly by an increased capillary hydrostatic pressure, in turn due to passively raised postcapillary resistance. Increased blood viscosity and platelet adhesiveness, cell aggregation, passive collapse of the veins, etc. seem to be factors contributing to this effect (Hardaway et al. 1962, Chien 1969, Ljungqvist 1970, Baeckström et al. 1971, Eriksson and Lisander 1972, Ericson and Eriksson 1973). In the intestine, an increase of capillary hydrostatic pressure is compatible also with the observed decline of vascular resistance (Fig. 8 A). Further, osmotically active substances (e.g. lactate) seem to be produced in the cells in late stages of bleeding, which also might lead to a fluid withdrawal from the interstitial, and secondarily from the intravascular, space. By extrapolation of the present data to man, the total transcapillary fluid loss can be calculated to amount about 175 ml after 90 min of hemorrhagic hypotension, of which the major part ($\approx$ 130 ml) occurred in the intestine.

It is likely that during hemorrhage in vivo the transcapillary fluid absorption might be somewhat larger, and the fluid filtration somewhat smaller, than in the present experiments, since central venous pressure then tends to fall as a consequence of the hypovolemia (cf. Schwinghamer et al. 1970, Grega et al. 1971). Return of extravascular fluid from skeletal muscle and skin to the blood stream via the lymph system apparently must be quite insignificant in view of the exceedingly small lymph flow that has been observed in these tissues under normal conditions at rest (cf. Jacobsson and Kjellmer 1964).

Chapter 7

AUTOREGULATION OF CAPILLARY HYDROSTATIC PRESSURE DURING REGIONAL ARTERIAL HYPO- AND HYPERTENSION

(Paper III,V)

General considerations

Hemorrhage is usually associated with a fall of arterial and central venous pressure. For a long time, the transcapillary fluid absorption in hemorrhage was believed to be caused solely by a passive drop of capillary hydrostatic pressure (p_c), secondary to these arterial and venous pressure alterations. To eliminate the effect on p_c of a possible fall of central venous pressure during hemorrhage, the present analysis of transcapillary fluid movements was performed under conditions of constant venous outflow pressure in the different regions. Arterial pressure, however, was reduced from the normal level to 50 mm Hg and it might be argued that this large pressure drop per se could have contributed to the transcapillary fluid absorption described in Chapter 6 via a passive decrease of p_c. However, as will be seen from the present analysis, such an effect is insignificant.

There are some previous observations which might be interpreted to indicate an approximate maintenance of the Starling fluid equilibrium in skeletal muscle when arterial inflow pressure is decreased (Mellander 1960, Folkow and Öberg 1961, Hanson and Johnson 1962, Lewis and Mellander 1962, Öberg 1964, Thulesius and Johnson 1966, Zweifach 1971), and such a phenomenon seems to be quite well established in the intestine (Johnson and Hanson 1962, Johnson 1968, Zweifach 1971, Haglund and Lundgren 1972, Fronek and Zweifach 1974, Gore 1974). Since skeletal muscle is the main target for the plasma volume control during bleeding, there was a need for a more systematic investigation of the influence of arterial alterations per se on the muscle transcapillary fluid exchange, and this was done in the present

study. In view of the fact that the arterial pressure in vivo varies considerably (Bevan et al. 1969), the analysis was limited not only to a pressure level of 50 mm Hg, but performed over the whole range from 30 to 170 mm Hg. Some observations were made in the paw as well.

Present results

Skeletal muscle. The effects on net transcapillary fluid movement of mechanically induced decreases of arterial inflow pressure were observed in the sympathectomized skeletal muscle with the plethysmographic technique. Similar studies were also made during arterial hypertension in the α-blocked region (see Methodology).

Fig. 9 shows the effects of short-term (≈ 5 min) regional arterial hypo- and hypertension on net transcapillary fluid movement, blood flow, and vascular resistance. The data are plotted versus regional perfusion pressure, venous outflow pressure being kept constant at about 5 mm Hg. It can be seen that such short-term periods of regional hypotension did not cause any significant transcapillary fluid movement, except in the lowest pressure range where, in fact, a slight fluid filtration was present. Arterial hypertension caused minute filtration. Above a perfusion pressure of 70 mm Hg, there was a fairly effective autoregulation of blood flow due to adjustments of regional vascular resistance.

There are no reasons to believe that tissue hydrostatic pressure or the transcapillary colloid osmotic gradient were significantly altered by the adjustments of arterial inflow pressure (for discussion, see paper V). From the data on fluid transfer (Fig. 9), the conclusion was therefore drawn that p_c remained approximately constant over the entire perfusion pressure range. It follows that the maintenance of p_c under these conditions must be attributed to adjustments of the pre-/postcapillary resistance ratio (r_a/r_v), see Fig. 10. For the calculation of r_a/r_v, p_c in the control period

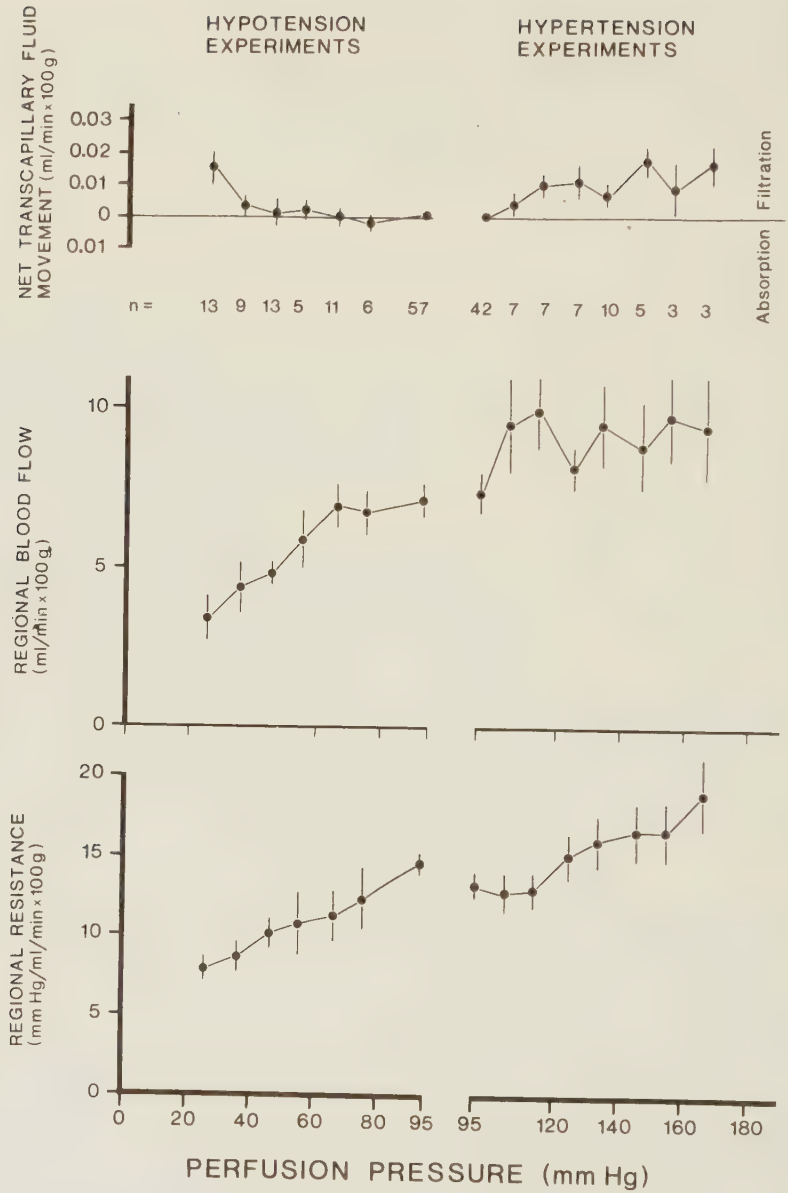

FIG. 9. Cumulated mean data ±S.E. on net transcapillary fluid movement and on resistance vessel responses during short-term regional arterial hypo- and hypertension in cat skeletal muscle. n indicates number of experimental observations.

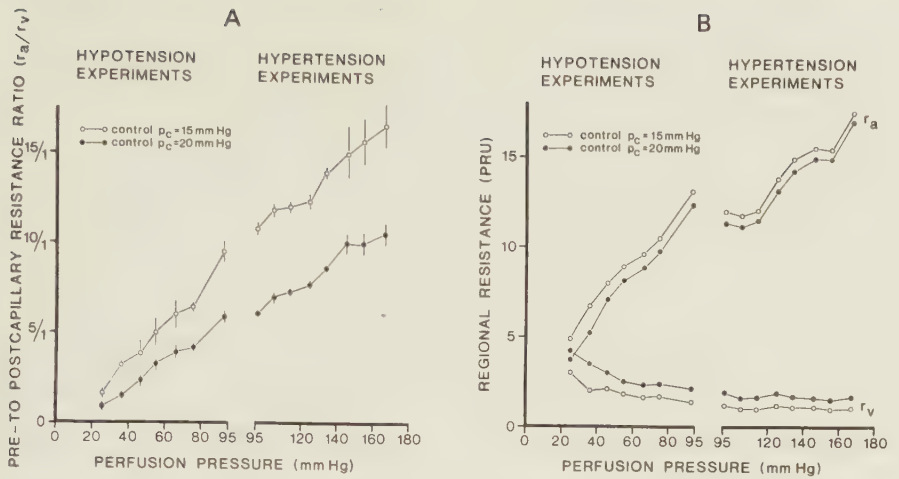

FIG. 10 A. Calculated ratios of pre-/postcapillary resistance (mean ±S.E.) during regional arterial hypo- and hypertension in skeletal muscle for assumed capillary hydrostatic pressures of 15 and 20 mm Hg, respectively, in the control period with normal perfusion pressure. B. Average precapillary (r_a) and postcapillary (r_v) resistances, expressed in absolute figures (mm Hg/(ml/min x 100 g)), during regional arterial hypo- and hypertension in muscle.

of normotension must be known (Pappenheimer and Soto-Rivera 1948). Recent studies indicate that normal p_c in the skeletal muscle at rest is in the range of 15-20 mm Hg (Diana 1970, Smaje et al. 1970, Lundvall 1972, Eliassen et al. 1974) and both these values were therefore used for the present calculations. It can be seen (Fig. 10) that r_a/r_v decreased below the control value during arterial hypotension and increased during hypertension (panel A) and that the alterations, except in the lowest pressure range, were mainly due to adjustments of precapillary resistance (panel B). The maintenance of p_c during changed arterial inflow pressure was accomplished by active "autoregulatory" adjustments of vascular tone, which was clearly demonstrated by comparing the results after abolition of vascular reactivity by papaverine infusions (paper V). In such a passive vascular bed, a de-

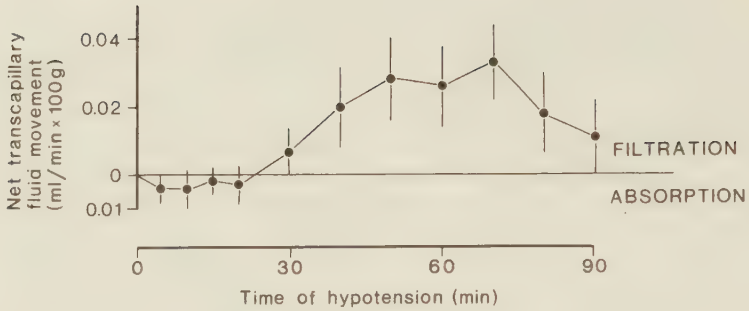

FIG. 11. Net transcapillary fluid movement in muscle during prolonged regional arterial hypotension at 50 mm Hg (mean ±S.E.).

crease of arterial inflow pressure led to a clearcut fall of p_c, as evidenced by a pronounced fluid absorption. - The fluid filtration observed in the lowest pressure range could be ascribed mainly to an increase of postcapillary resistance (see Fig. 10 B), apparently caused by "passive" factors, such as venous collapse and cell aggregation (e.g. Eriksson and Lisander 1972).

Observations of transcapillary fluid shifts during prolonged (90 min) regional hypotension at 50 mm Hg were also made (Fig. 11) in order to permit correct interpretation of the capillary fluid movements described in Chapter 6. Such prolonged hypotension did not cause any significant transcapillary fluid movement in the first 30 min, but, after that, a moderate fluid filtration (0.01-0.04 ml/min x 100 g) was present. It is therefore concluded that the fluid absorption occurring in early stages of hypotension cannot be attributed to the arterial pressure fall per se, but must be due to the described reflex and osmotic mechanisms. As discussed above, the later fluid filtration apparently must be ascribed to a passive increase of the postcapillary resistance.

Skin. Vascular resistance and net transcapillary fluid exchange were observed in the sympathectomized paw in response to prolonged (90 min) hypo-

tension at 50 mm Hg in 2 experiments (III). Such a regional hypotension caused an abrupt increase of cutaneous vascular resistance of similar magnitude to that observed in the hemorrhagic hypotension experiment (cf. Fig. 8 A) suggesting that the resistance increase was a "passive" event. The regional hypotension led to a moderate fluid filtration (0.02-0.05 ml/min x 100 g) already in the early stage of hypotension, suggesting that, in relative terms, this passive resistance increase was especially confined to postcapillary vessels. It may therefore be concluded from these experiments that the osmotic fluid absorption observed in skin during hemorrhagic hypotension (Chapter 6), if anything, has been somewhat underestimated.

Comments

Evidence has been presented which demonstrate an efficient autoregulation of capillary hydrostatic pressure in skeletal muscle over a wide range of regional arterial hypo- and hypertension. The phenomenon may be conceived of as a complement to the previously well established autoregulation of blood flow (see Johnson 1964), both effects apparently aimed at a maintenance of the circulatory homeostasis in the tissue. The preservation of p_c is accomplished by local control systems adjusting vascular tone and it appears that metabolic as well as myogenic mechanisms contribute to the reaction. It might be argued that this autoregulation is less effective during hemorrhage in vivo, when the vascular bed is under more pronounced influence of the adrenergic nerves (cf. Folkow et al. 1964). Direct observations (Lundvall, unpublished) indicated, however, that the described autoregulation of p_c was well preserved during sympathetic nerve stimulation to skeletal muscle.

The present results can be interpreted to indicate that the arterial pressure fall per se was not responsible for the observed transcapillary fluid absorption in hemorrhage.

Arterial pressure in normal life is subjected to considerable fluctuations (e.g. Bevan et al. 1969), and the described autoregulation of p_c can therefore be considered an important mechanism which prevents gross, undue fluid redistributions between the intra - and extravascular compartments. When, as in bleeding, a vital demand for an absorption of extravascular fluid to the blood stream does exist, this process is governed by special control systems, viz. via the reflex adrenergic and osmotic mechanisms.

Chapter 8

EFFECTS ON REGIONAL VASCULAR RESISTANCES EVOKED BY INCREASED BLOOD OSMOLALITY

(Paper VI)

General considerations

The hyperosmolality which develops in some tissues as a result of increased metabolism can cause pronounced dilatation of the regional resistance vessels. Thus, tissue hyperosmolality has been shown to be an important mediator of functional vasodilatation in exercising skeletal muscle (Mellander et al. 1967, Lundvall 1972) and in secreting salivary glands (Lundvall and Holmberg 1974). The vascular smooth muscle in several other tissues than muscle and glands is also responsive to hyperosmolality, which has been shown by intra-arterial hypertonic infusions to the lung (Hauge and Bø 1971), myocardium (Gazitùa et al. 1971), adipose tissue (Sachs et al. 1971), gut (Lucas and Read 1966, Van Heerden et al. 1968, Lundvall 1972), kidney (Navar et al. 1966, Gazitùa et al. 1969, Young and Rostorfer 1973) and brain (Johnston and Harper 1973, cf. Wahl et al. 1973). In several of these studies, however, the induced hypertonicity can be considered 'supraphysiological'.

In the present study an attempt was made to evaluate in quantitative terms the changes of vascular resistance in different tissues evoked by a generalized blood borne hyperosmolality of similar magnitude to that in hemorrhage. This was done by studying cardiovascular effects of graded intravenous infusions of hypertonic solutions in non-bled animals.

Results

Hypertonic solutions of glucose, sucrose, or xylose were infused intrave-

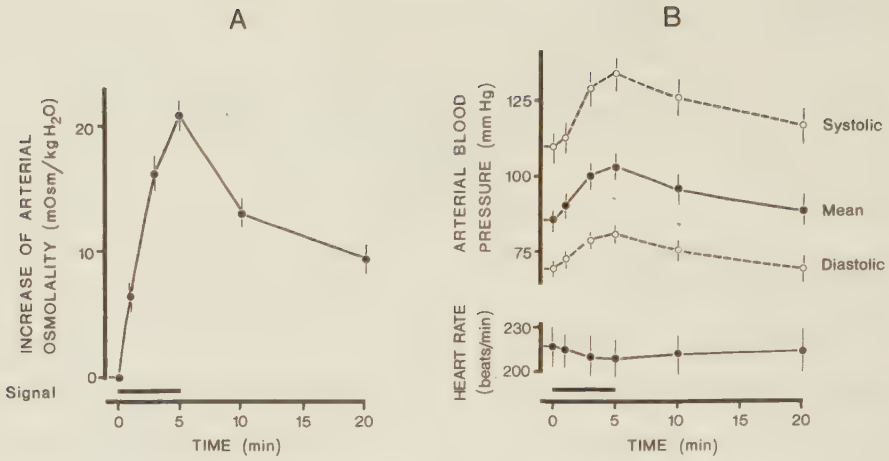

FIG. 12. Increase of arterial plasma osmolality above the control level (panel A), and changes of systolic, mean, and diastolic arterial blood pressure, and of heart rate (panel B) evoked by intravenous hypertonic infusion (signal). Mean values ±S.E. are given for 30 infusion experiments performed in 14 cats.

nously during 5 min into the non-bled animal at such rates that an increase of arterial plasma osmolality of about 20 mOsm/kg H_2O gradually developed (Fig. 12 A, reproduced from paper VI).

These infusions evoked significant changes of blood pressure and regional blood flows co-ordinated in time and magnitude to the osmolar change, whereas the effects of corresponding isotonic infusions were negligible. During the peak rise of osmolality after 5 min, the systolic pressure increased by 18 mm Hg, the diastolic pressure by 5 mm Hg and, thus, the pulse pressure by 13 mm Hg (Fig. 12). Heart rate, if anything, tended to decline. There were concomitant increases of the regional blood flow in skeletal muscle, skin, kidney, and intestine both in the intact and the sympathectomized regions, the effects being somewhat more pronounced in the latter situation (Fig. 13, reproduced from paper VI). These augmentations of regional blood flow to some extent was due to the increased perfusion pres-

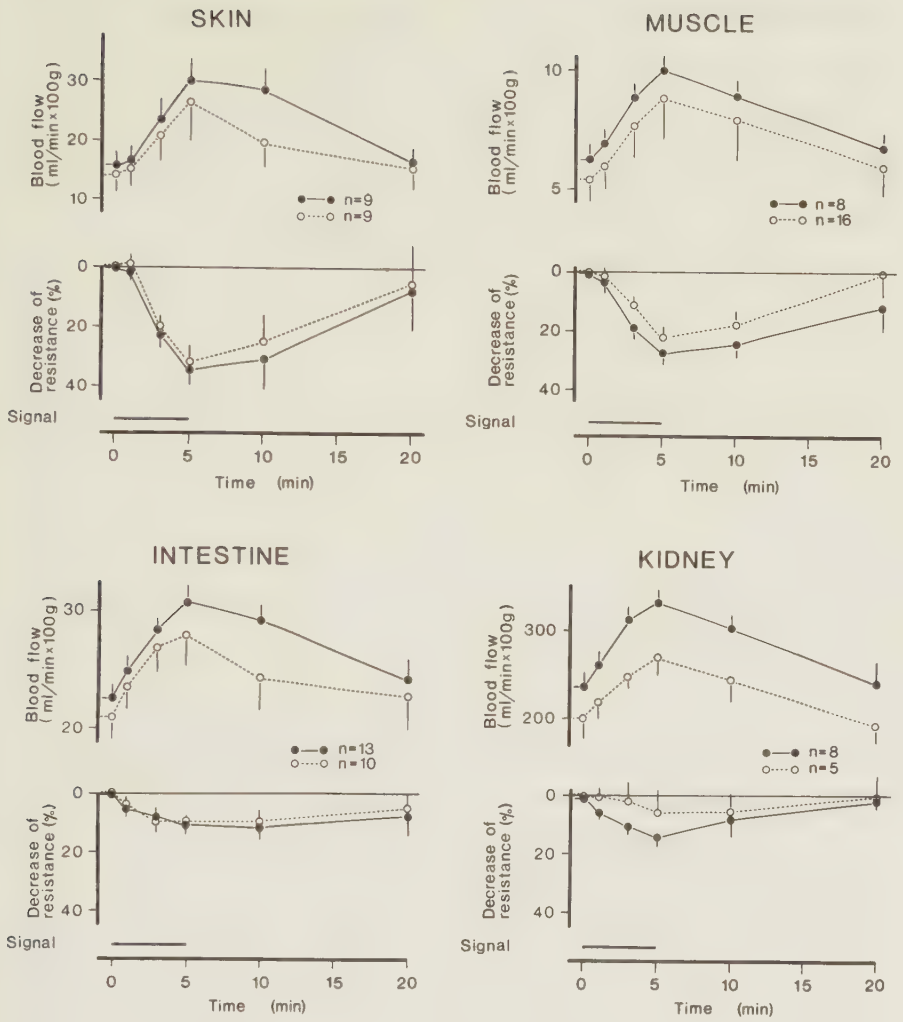

FIG. 13. Effects of i.v. hypertonic infusion (signal) on the regional blood flow and vascular resistance in intact (o---o) and sympathectomized (●——●) vascular beds of skin, skeletal muscle, intestine, and kidney. Mean values ±S.E. are given. The concomitant average changes of arterial osmolality and blood pressure are depicted in Fig. 1.

sure, but the effect was mainly caused by a decreased vascular resistance, ranging from 10-30 % in the different regions (Fig. 13). In relative terms, the resistance decrease was most pronounced in skin and skeletal muscle.

The fact that the vascular resistance decrease was present in the sympathectomized regions, and also after β-adrenergic blockade by propranolol (1 mg/kg b.wt.), indicated that the effect was caused by a direct inhibitory action of the hyperosmolality on the vascular smooth muscle (see below). The blood pressure response to hypertonicity, however, was depressed by about 40 % by propranolol which suggested that the effect of hyperosmolality on the heart was partly mediated via cardiac β-adrenoceptors (see further below).

Comments

The presents results showed that experimentally induced blood hyperosmolality of similar magnitude to that occurring in severe hemorrhage (Chapter 3) and in heavy exercise (Lundvall et al. 1972) can evoke a moderate dilatation of peripheral resistance vessels, probably by a direct action on the vascular smooth muscle. The mechanisms responsible for the inhibitory action of hyperosmolality on vascular tone have been studied in vitro (Mellander et al. 1967, Johansson and Jonsson 1968, Arvill et al. 1969, Johansson 1969). These investigations have shown that the smooth muscle relaxation could be ascribed mainly to inhibition of myogenic pacemaker activity, in turn due to changes in transmembrane ionic concentration gradients and in membrane permeabilities produced by osmotic reduction of smooth muscle cell volume. It cannot be excluded, however, that part of the resistance decrease was due to rheological phenomena, i.e. a lowered blood viscosity caused by absorption of extravascular fluid.

The osmotically induced increase of arterial blood pressure in face of

vasodilatation in four hemodynamically important vascular beds indicates an enhancement of cardiac output, in turn due to an increased stroke volume, since heart rate was unchanged. The increased plasma volume caused by osmotic transcapillary fluid absorption (Chapter 6) quite likely contributed to the observed blood pressure rise, and then, mainly via an interference with the Frank Starling mechanism. The cardiac effect, at least in part, also might be attributed to a direct positive inotropic action of hyperosmolality, a hypothesis which gains support from previous more detailed investigations both in vitro and in vivo (Koch-Weser 1963, Wildenthal et al. 1969a,b, Templeton et al. 1972, Atkins et al. 1973). The attenuated blood pressure response to hyperosmolality after β-blockade suggests that the cardiac effect to some extent also was mediated via β-adrenoceptors, an opinion corroborated by the studies of Wildenthal et al. (1969a). That hyperosmolality can lead to a centrally mediated increase of sympathetic discharge has recently been shown by Mellander and Hillman (1975) and Schad and Seller (1975).

It may be concluded that hyperosmolality is a factor which can contribute to the overall cardiac adjustments in hemorrhagic hypotension, but simultaneously tends to oppose the reflex peripheral vasoconstriction.

The described effects were evoked by what can be considered to be a "physiological" increase of blood osmolality. The pattern of response to hyperosmolality can be different when drastic, rapid increases of blood tonicity are experimentally induced. Under these circumstances, a bradycardia and arterial hypotension most commonly develops (e.g. Binet and Stoicesco 1929, Muirhead et al. 1947, Read et al. 1960), but some authors have reported different neurogenic vascular resistance responses mediated via central or peripheral receptors (Holland et al. 1959, Lasser et al. 1960, Agarwal et al. 1969, Inglesby et al. 1972, Raizner et al. 1973).

Chapter 9

GENERAL CONCLUSIONS

The aim of the present investigation was to define blood osmolality changes during hemorrhagic hypotension, their underlying mechanisms, and their importance for circulatory adjustments in hypovolemia. The experiments were performed on anesthetized cats exposed to standardized rapid bleeding to a constant arterial pressure level of 50 mm Hg. The following main conclusions were drawn:

1. Hemorrhage caused a rapid increase of arterial plasma osmolality reaching a level about 20 mOsm/kg H_2O above the control value after 20 min. This plateau was then maintained throughout a hypotension period of 3 hours. The osmolality in peripheral venous blood rose more gradually implying the existence of a positive arterio-venous osmolar difference during the early stage of hypotension.

2. A pronounced hyperglycemia developed during hemorrhage and its magnitude was such as to almost fully account for the blood hyperosmolality during the first hour of hypotension. Electrolyte changes also occurred, but in opposite directions (e.g. decreased sodium and increased potassium concentrations), so that the net effect of such alterations on total plasma osmolality was small.

3. The hemorrhagic hyperglycemia was caused by glucose release from the liver, in turn mediated via three different reflex mechanisms: by direct sympathetic nervous influence on the liver, by glucagon released via the sympatho-adrenal system, and by catecholamines emanating from the adrenal medulla.

4. Quantitative analysis of capillary fluid exchange in skeletal muscle revealed a considerable transcapillary absorption of extravascular fluid into the blood stream during the first hour of hemorrhagic hypotension.

Such fluid transfer occurred not only in the intact muscle region, but also after regional α-adrenergic blockade and sympathectomy, showing that mechanisms other than the previously known adrenergic reflex resetting of the pre-/postcapillary resistance ratio contributed to the fluid absorption.

5. This fluid absorption could not be attributed to a passive fall of capillary hydrostatic pressure (p_c) caused by the arterial hypotension per se, since p_c was shown to remain virtually constant at the normal control level when arterial inflow pressure to the muscle region was mechanically varied over the whole range from 30 to 170 mm Hg in non-bled animals. This maintenance of p_c was accomplished by local autoregulatory adjustments of precapillary vascular tone, causing a resetting of the pre-/postcapillary resistance ratio.

6. The fluid withdrawal was not due to a fall of regional venous pressure, since this was kept constant in the present experiments. Nor could it be ascribed to the effects of humoral vasoconstrictor agents such as angiotensin or vasopressin.

7. The rate and time-course of the transcapillary fluid absorption in the sympathectomized and α-blocked muscle region were distinctly related to the observed arterio-venous osmolar difference (reflecting the transcapillary osmolar gradient). Absorption at similar rates to those observed in hemorrhage was evoked in the sympathectomized muscle region in non-bled cats in response to hypertonic glucose infusions, which raised plasma osmolality to the same levels as in bleeding. The conclusion was reached that the described capillary fluid transfer was an osmotic process caused by the arterial hyperosmolality (hyperglycemia).

8. Osmotic withdrawal of extravascular fluid also occurred in skin and intestine during hemorrhage. This effect, especially in the intestine, was less pronounced than in skeletal muscle.

9. The transcapillary absorption of extravascular fluid from skeletal

muscle is of great hemodynamic importance in hemorrhage insofar that it helps to restore plasma volume. The present data indicated that, in the intact organism, the adrenergic reflex and the osmotic mechanisms are both important for this plasma volume control, the former mechanism being especially effective in the initial stage of hemorrhagic hypotension. Extrapolation of our data on capillary fluid transfer to man suggests that a total extravascular fluid volume of about 650 ml would be absorbed into the blood stream from all skeletal muscle tissue within the first hour of hemorrhagic hypotension. The osmotic mechanism would be responsible for at least 50 % of this effect.

10. It appears that the described osmolar control system is basically aimed at an overall regulation of extracellular fluid volume in hemorrhage, insofar that it causes a glucose-osmotic fluid (water) withdrawal from the intracellular compartment. The consequent dilution of proteins in the interstitial space of the tissues can help to explain why the osmotically and reflexly absorbed protein-poor extravascular fluid from skeletal muscle and skin is retained for considerable length of time within the circulatory system.

11. In later stages of hemorrhage, some plasma fluid was lost by filtration into skeletal muscle, skin and intestine, an effect most pronounced in the latter tissue.

12. In addition to the effect on fluid redistribution, the hemorrhagic hyperosmolality was found to exert a positive inotropic action on the heart and a moderate dilator effect on the resistance vessels in skeletal muscle, skin, intestine, and kidney.

It appears from this and previous studies that the organism, with regard to its volume control, has several defence mechanisms against hemorrhagic hypovolemia: a. Reflex adrenergic constriction of the capacitance vessels

tends to adapt almost instantaneously the size of the intravascular space in relation to the decreased blood volume, and this effect is co-ordinated with reflex adjustments of cardiac performance and peripheral resistance. b. Reflex adrenergic resetting of the pre-/postcapillary resistance ratio leads to withdrawal of interstitial fluid from muscle tissue into the blood stream, hence increasing the plasma volume. c. The reflexly induced glucose-osmotic mechanism tends to restore extracellular fluid volume by water re-distribution from the intracellular space, and, in addition, it increases the plasma volume by net transcapillary fluid movement from skeletal muscle d. By activation of the thirst mechanism and adjustments of renal excretion, the overall fluid balance in the body tends to be restored. e. Finally, there is a gradual restitution of the red cell volume, mainly effected by the erythropoietin mechanism.

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